BIOPHARMACEUTICAL DRUG DEVELOPMENT MODELING AND PORTFOLIO MANAGEMENT

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by

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To my parents with love and gratitude

ABSTRACT

Current pressures of cost and speed to market are driving the need for more effective means of assessing the value and risks of drug portfolios. This thesis presents research to generate a prototype computer-aided tool to predict the process and business outcomes for portfolios of biopharmaceutical drugs proceeding through the development pathway. The tool was built using a discrete-event simulation package, thus facilitating the dynamic nature of drug development decisions to be captured. The framework uses a hierarchical approach to incorporate the interactions between drug development activities, the available resources and databases of information. In addition to the business and process issues, the risks involved in the process of drug development have also been incorporated into the tool.

The application of the tool for assessing drug portfolios under uncertainty is demonstrated via case studies. In the first, the tool was used to perform sensitivity and scenario analysis on the portfolio net present value (NPV). Contour plots were generated that provide the ability to plan for a range of contingencies including uncertainties in manufacturing efficiencies, product demand and the market share captured. The second case study was used to assess the impact of different manufacturing strategies on the portfolio NPV under uncertainty. This example was based on a biopharmaceutical company considering whether to risk building a facility for the commercial manufacture of its antibodies and if so, when to start building, or whether to rely on a contract manufacturer throughout the development cycle and market manufacture. The effects of uncertainties were analysed using Monte Carlo simulation methods. The study highlighted the benefits of incorporating uncertainties when ranking different strategies. The third case study looked at the selection of drug candidates for a drug portfolio. The risk and reward of different portfolios were computed using Monte Carlo simulations. The 'Efficient Frontier' method was used to select an optimal portfolio.

The thesis illustrate the benefits of using such a tool to investigate the uncertainty and value of different development strategies and to assist in the process of decision-making in the context of both business and process aspects.

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ABBREVIATIONS

ADMET - Absorption Distribution Metabolism Excretion Toxicology

BLA – Biological License Application

CBER - Centre for Biologics Evaluation and Research

CDER - Centre for Drug Evaluations and Research

cGMP – Current Good Manufacturing Practice

COG – Cost of Goods

CMO – Contract Manufacturing Organisation

CRO – Clinical/Contract Research Organisation

EMEA – European Medicines Evaluation Agency

FTC – Federal Trade Commission

IND – Investigational New Drug

MAB – Monoclonal Antibody

MHRA - Medicines and Healthcare products Regulatory Agency

MILP – Mixed Integer Linear Programming

NDA – New Drug Application

NPV – Net Present Value

R&D – Research and Development

TCT – Time Compression Technology

US FDA – United States Food and Drug Administration

CHAPTER 1

SCOPE AND BACKGROUND

1.1 INTRODUCTION

The rapid growth of the biotechnology industry as a provider of high technology, highly specific and effective new medicinal therapies has been profound. The ability to modify genetically living organisms to produce a range of medicines has contributed to a plethora of biopharmaceuticals being developed. The biotechnology industry as we know it today was borne with the founding of Genentech in 1976 and from that early and singular beginning, the number of companies focussing exclusively on biological products and processes has increased globally to more than 5,500 today (Sager, 2001). In 2000, 28 major protein-based products generated $13.3 billion of sales and in 2002 there were 99 protein-based therapeutics in Phase II and Phase III clinical development (Ginsberg *et al.*, 2002).

The biopharmaceutical industry faces mounting competitive pressures of cost reduction whilst increasing speed to market (Pisano and Wheelwright, 1995). The process of bringing these products to the market is a costly and risky one. On average it takes 7.7 years to bring a pharmaceutical product to market (Foo *et al.*, 2001) and costs over US$ 800 million (DiMasi *et al.*, 2003). This cost of research and development (R&D) for new drugs has been on the rise for the past two decades (DiMasi *et al.*, 2003; Halliday, 1996). Speed to market and pressure to reduce costs are critical factors driving the need for more effective means of assessing the value and risks of such drug portfolios.

In order to aid decision-making, the management that is in charge of designing and implementing development plans has to be able to compute the reward and risk of different options and routes of drug development. By reference various methods are used by the pharmaceutical industry for product portfolio management. Popular financial models used by companies include net present value, decision trees, option

models and computer simulations (Soegaard, 2003). To address the question of managing biopharmaceutical drug development more effectively, a closer integration of the drug development activities and business process modelling is vital. The application of computer-aided design tools can help to achieve the objectives of accelerated drug development, reduce costs and ensure minimum investment loss due to drug candidate failure during the drug development process. This thesis investigates the possibility of developing a prototype software tool that accomplishes this integration and then explores the utility of such a tool in decision-support.

The purpose of this chapter is to review the management of the drug development process and the new product portfolio management of biopharmaceuticals. This introductory material provides an overview of biopharmaceutical drug development and reports on the current status of drug portfolio management. Section 1.2 provides a brief introduction into the key drivers and pressures in biopharmaceutical drug development. Section 1.3 introduces the portfolio management process deployed within the industry to manage drug portfolios and assist in decision-making regarding drug development activities. The methods used in executing portfolio management are discussed in Section 1.4. The process and challenges of modelling drug development are presented in Section 1.5. Methods of performing risk analysis are discussed in Section 1.6. Finally the aims and organisation of the thesis are presented.

1.2 BIOPHARMACEUTICAL DRUG DEVELOPMENT

A comprehensive description of the biopharmaceutical drug development process is presented in Chapter 2 of this thesis. The objective of this section is to provide a brief overview of the lengthy and costly process of drug development in order to emphasise the importance of decision-making and portfolio management during the drug development process. The world market for protein drugs was estimated at US$ 41 billion at the end of 2002 (Ernst and Young, 2003). By 2010 the worldwide biopharmaceutical market is expected to capture 50% of the pharmaceutical market (Savage, 2000). At the end of 2002 there were 130 such products (therapeutic as well as diagnostic) in the market and over 350 at different stages in clinical development (Burrill and Company, 2004a).

This very positive image has to be considered against the harsh commercial realities. Over the past three decades, pressures from international markets and tough government policies have created difficult business conditions for the pharmaceutical industry (Gatica, 2003; Partington, 2000). Traditionally, the drug development process has been a lengthy and expensive series of non-clinical and clinical evaluations followed by regulatory reviews (Clemento, 1999). Every drug in a pharmaceutical product portfolio undergoes a well-defined development process (Figure 2.1). During this process of development, candidates fail due to safety, efficacy or commercial reasons. For every approved drug, roughly 10,000 molecules have started development and have been abandoned along the way (Carr, 1998).

The financial value of pharmaceutical drug developmental projects is difficult to assess because they are subject to considerable uncertainty (Rogers *et al.*, 2002). This uncertainty lies in both the technical and market aspects of the project. The technical uncertainty refers to the aforesaid toxicity, efficacy, dosage and the manufacturing process. Market uncertainty concerns the volatility of the market as forecasted during the early research and development stages. Quelin (2000) provides a description of the technical and market uncertainties in the area of new product development in general. Tiggeman *et al.* (1998) provides a further breakdown of the uncertainty in product development in the pharmaceutical industry into four categories, which are interrelated. These are customer, technological, competitive and resource uncertainty.

The management of pharmaceutical research and development has become increasingly difficult in recent years and the need for more effective strategies and management practices has become greater (Halliday, 1996). Pharmaceutical companies are constantly faced with the question of how best to use the limited resources available to obtain the highest possible profit and the decisions involved are usually taken in the presence of significant uncertainty (Levis and Papageorgiou, 2004). Late investment decisions could cause the pharmaceutical company a significant loss of revenue due to loss of patent time. Therefore the luxury of waiting for research and development work to be completed in order to make well-informed decisions is not afforded to the pharmaceutical companies.

The typical decisions that a pharmaceutical company has to make during the process of the lengthy uncertain drug development process are:

- Which drug candidates are to be developed and which ones are to be dropped from the portfolio or be held back for future development
- Which candidates receive prioritisation in resource allocation
- How should resources be allocated for development work
- What manufacturing strategy should be employed in order to have material ready for clinical trials and consequently for the market.

The rewards and risks of drug development have to be quantified in order to make the best decisions. Investment into R&D activities alone does not guarantee success, as shown by the high failure rate of products and services that do not make it through to commercialisation. A robust process for decision-making should exist within an organisation in order to make strategically the best decisions that will add value to the product portfolio and help to contain the risk. However, most organisations view decision–making as an event and not a process (Sharpe and Keelin, 1998). R&D portfolio management should be an integral part of corporate culture and business processes of pharmaceutical companies (Tiggeman *et al.*, 1998). The next section describes the process of portfolio management deployed in order for proper decision-making in the pharmaceutical industry to be achieved.

1.3 PORTFOLIO MANAGEMENT

High quality decisions about long-term business strategy often require the explicit analysis of uncertainty. Portfolio management is an established business process that is linked with other business processes including strategic planning and budgeting. Through portfolio management, decision-making and resource allocation are measurably improved. Keelin and Shew (2003) state that portfolio management is justified by a one-hundredfold return on investment.

Research and development (R&D) management, by its very nature, is characterised by uncertainty since effective R&D requires a complex interaction of variables (Doctor *et al.*, 2001). It is important to balance strategic management (allocate resources and do the right R&D) with operational management (execution of projects) and at the same time take into account issues of people management

(leadership, motivation, organisation and teamwork) (Menke, 1994). Portfolio management has progressed through three generations in the biopharmaceutical industry, ranging from early management science tools in the 1980s, through resources allocation techniques in the early 1990s, to the high-powered, value-adding business processes that some companies are using currently (Keelin and Shew, 2003). The authors describe the evolution of portfolio management in the biopharmaceutical industry (Table 1.1).

An exploratory investigation into portfolio management practices found that one main goal of R&D portfolios is to achieve the right balance and mix of projects (Cooper *et al.*, 1997). By diversifying the therapeutic areas, disease states and discovery platforms in research and development, a company can reduce its risk (Tiggemann *et al.*, 1998).

As a vital part of portfolio management, companies identify potentially profit-making products on an ongoing basis seeking to maximise return on investment (Soegard, 2003). Tiggemann *et al.* (1998) identify four key areas, safety, efficacy, patient convenience and economics, in which some advantage must be found in order to justify a new strategy. Sharpe and Keelin (1998) describe how SmithKline Beecham increased the value of its portfolio by 30% through a new decision-making process without increasing its spending on R&D. This outlines the contribution of a proper decision-making strategy to increasing a company's value both in the long and short term.

Loch (2000) details a study into whether general best practices in decision-making in new product development can be applied to a specific company and concludes that there is no such best practice and each company should develop a unique new product portfolio management strategy. Portfolio management applies to all areas of drug development. During the drug discovery stages the targets and mechanisms that are to be pursued have to be decided in line with the company's strategy. In the clinical development stages one of the key issues would be to decide the prioritisation of products for allocating limited levels of resources. Manufacturing capacities and sales strategies have to be decided and applied at the front end of the drug development pathway.

Table 1.1 Comparison of three generations of portfolio management (Keelin and Shew, 2003)

	First generation	Second generation	Third generation
Purpose	Learn	Solve problems	Create new value
Perspective	Experiment	Minimise cost	Maximise return on investment
Impact on decision-making	None	Very little for most companies	Significant, identifiable directional changes
Value added	None	Rarely measurable Mixed perceptions	Real, measurable Sustained advantage
Role of staff	Isolated	Provide useful inputs	Lead decision-making process Fully engage key players
Line management engagement	Not visible to line management	Not totally involved	All key players committed
Business process	None	Established, feeds budgeting	Well interlinked with business and TA strategies, budgeting
Era (for most)	1980s through mid-1990s	Mid-1990s to present	Now emerging

High quality valuation methods have to be applied to capture the risks and rewards implicit in applying different options in R&D projects. By being able to compute and then compare the array of possible outcomes and key sources of uncertainty, management is provided with a key tool to manage and balance the portfolio. Effective portfolio analysis can identify the optimal portfolio in terms of value creation for any given set of constraints. Soegaard (2003) in outlining the challenges faced in drug portfolio management points out that integrating information from marketing and R&D is a major challenge facing the task of portfolio management.

The author further states that the integral challenge of comparing projects at different development stages and difficulties of quantifying uncertainties in development are likely to remain major challenges in the near future. One of the most acute challenges inherent in decision analysis is the actual measurement of uncertainty in historical data (Soegard, 2003). For example Senn (1998) in describing the statistical issues in project prioritisation cites the task of predicting project failure rates as one of the biggest practical problems faced in applying decision analysis. Research into failure rates of pharmaceuticals is reviewed in Section 2.4.3. The models chosen for application in decision analysis influence both the final outcome as well as a company's perception of the options and uncertainties that confront them (Soegaard, 2003).

1.4 METHODS USED FOR PORTFOLIO MANAGEMENT

Strategic project management is a complex, value-creating process to assure long-term corporate success, and hence there is a need for techniques to act as value creation facilitators (Asrilhant *et al.*, 2004). Traditional portfolio evaluation models often rely on qualitative and semi-quantitative tools. New quantitative methods have been developed that compute directly how much value decisions add to an R&D portfolio (Keelin and Shew, 2003).

Strategic decision-making and portfolio management is applied right through many industries. This is reflected in the literature. Gittins (1996) reviews the quantitative methods in the planning of pharmaceutical research. Asrilhant *et al.* (2003) describes the best practices in decision-making in strategic project management, as applied to the upstream oil and gas sector. Raz *et al.* (2002) presents the results of an empirical study into risk management tools and techniques across many industries. The authors focus on the relationship between the project types and the application of risk management practices.

The methods used in portfolio management are a combination of mathematical, managerial and financial approaches. Over two hundred qualitative and quantitative models exist in the literature for R&D project selection; including financial models, checklist models, decision theory models, consensus models and portfolio models (Coffin and Taylor, 1996). A wide range of literature exists in decision-making in

new product development. Doctor *et al.* (2001) provides a review of the financial methods used in the industry for managing uncertainty in research and development. Chien (2002) provides an extensive literature review of some of the early methods used in portfolio selection. The author divides the portfolio attributes into independent and interrelated categories. Independent portfolio attributes are those to which the contribution of each project is independent of the other projects. Interrelated portfolio attributes are those to which the contributions of the projects are interrelated. Kengpol and Brien (2001) describe the development of a decision support tool to assess the value of investing in Time Compression Technologies (TCTs) to achieve rapid product development. Time compression technology refers to any technology that can improve a design and manufacturing process to achieve better quality in a shorter period, such as rapid prototyping. The authors propose a decision support tool that integrates a cost/benefit analysis model, a decision-making effectiveness model and a common criteria model in order to select the most appropriate time compression technology for an organisation.

Next the different methods applied in portfolio management are reviewed. Most of these methods use the net present value (NPV) as the main indicator of profitability. The methods comprise of quantitative as well as qualitative approaches.

1.4.1 Checklists, scorecards and indices

The simplest and most widely used project selection techniques are check lists and project profiles which are sometimes extended by scoring systems to provide overall scores, giving a ranking between projects (Gittins, 1996; Tiggemann *et al.*, 1998). These qualitative scoring systems are used to provide an overall score, which is then used to rank projects. Senn (1998) reviews the various aspects of portfolio management within the pharmaceutical industry and describes the use of a risk-reward grid for comparing different projects. Profitability indices, for example, by dividing expected revenue by expected cost, in principle are not the right criteria (Tiggemann *et al.*, 1998). This is because the profitability indices have the property that a portfolio, which is made up of projects with larger indices than those of the possible projects that have been rejected, produces the highest possible income for a given expenditure expressed in terms of total expected cost (Gittins, 1996).

1.4.2 Balanced scorecard

Introduced by Kaplan and Norton (1992) the Balanced Scorecard is an organizational framework for implementing and managing strategy at all levels of an enterprise by linking objectives, initiatives, and measures to an organization's strategy. The scorecard provides an enterprise view of an organization's overall performance. It integrates financial measures with other key performance indicators around customer perspectives, internal business processes, and organizational growth, learning, and innovation. Bremser and Barsky (2004) conclude that the balance scorecard method provides a basis for linking financial and non-financial performance measure for managing R&D activity. The authors discuss the usefulness of the balance scorecard method for seven performance measures and conclude that the balanced scorecard method could be used effectively by professionals in all functional areas.

1.4.3 Decision trees

Decision trees are mentioned in the literature to help understanding the project path, the probabilities of success, developing project gates and facilitating the calculation of revised probabilities of success as the project progresses (Doctor *et al.*, 2001). One of the main disadvantages of decision trees is the inability to capture processes that are occurring in parallel in a meaningful way. Sharpe and Keelin (1998) used decision trees to address the resource allocation issues at SmithKline Beecham by proposing to seek alternatives to current projects. The alternatives included scaling up as well as scaling down the current status of the project. The authors claim that by explicitly modelling the alternatives and involving all the staff in the decision-making process the company managed to increase the value of the portfolio by 30%.

1.4.4 Reviews

Organisational ability and capability has been cited as a key area for improving the management and planning of R&D activities. Islei *et al.* (1991) presents a detailed application of R&D portfolio modelling in the pharmaceutical industry through a judgmental model that allows detailed performance appraisal of project managers. Lilly and Porter (2003) presents research examining how organisations can use improvement reviews to enhance learning from product development experiences. The authors conclude that through reviews people-related problems could be reduced and it provides an insight into improving the best practices in product development.

Thamhain (2003) reviews the management of innovative R&D teams and attempts to provide an insight into the type of organisational environment and managerial leadership that is conductive to innovative R&D team performance.

Gerson *et al.* (1998) describes a management tool developed by Wyeth-Lederle Vaccines and Pediatrics to increase the success rate of transfer of new biological processes from research and development to manufacture. The tool was designed to streamline the technology transfer through better communication and documentation. The outlined decision-support system provides the basis for monitoring the progression of the projects. Each aspect of the business process beginning with the discovery of a new drug to the launch of the new product is dissected into a hierarchical sequence of business unit operations and each of them analysed separately. The combined set of analyses provides, in effect, a dynamic model of the business showing the sequence of events and the rates and routes of flow of materials and information.

1.4.5 Financial methods

Markowitz (1952, 1991) proposed the portfolio theory, which was mostly aimed at the financial portfolio of stocks and securities. This method is explained further in detail in Chapter 6.

Osawa and Murakami (2002) proposed a new methodology of evaluating industrial R&D projects to assess the effectiveness of future R&D in terms of financial credibility, to prioritise them efficiently by clear criteria to reduce the time and burden consumed by both project leaders and management staff. Three quantitative criteria, sales, profit and R&D efficiency are used along with three qualitative criteria, strategic importance, technological effect and probability of realisation. The authors demonstrated the method through a case study in the electronics industry.

1.4.6 Optimisation methods for scheduling R&D

Many mathematical methods for new product selection and resource allocation can be found in the chemical engineering literature. However these usually result in complex mathematical methods where a high level of knowledge is required for application. Such methods have been applied mostly to chemical entities and agro-

chemicals. By contrast little attention has been paid to biopharmaceuticals. Shah (2004) discussed the key issues and strategies for optimising the pharmaceutical supply chain as a whole. The author describes the life cycle of pharmaceutical and outlines the different decisions that have to be made at each stage. This is followed by an extensive review of the literature of recent work carried out in this area of optimisation.

A numerical method, where multiple criteria were used for R&D project selection was presented by Coffin and Taylor (1996). Schmidt (1996) presented a stochastic optimisation model to improve production planning and R&D resource allocation in biopharmaceutical production processes. The proposed model was a Markov decision process model that combined the features of engineering design models and aggregate production planning models to obtain a hybrid model that links biological and engineering parameters to optimise operations performance.

The task of scheduling R&D tests and the manufacturing process through the scheduling of batch processes are also covered within this field. Schmidt and Grossman (1996) addressed the problem of optimising the schedule of testing tasks without resource constraints or task success uncertainty in the process of new product development. This was limited to a single project. The problem was formulated as a mixed integer linear program (MILP) problem and allowed up to 19 tasks to be scheduled and when solved maximised the net present value (NPV) of the project. The authors stated that each optimised project would add up to an optimised portfolio. It was suggested that a two level hierarchical approach be made to project selection. At the top level resources are allocated to different projects and then on the next level the testing tasks are scheduled to stay within the allocated resources.

Honkomp (1998) addressed both project selection and project scheduling with task success uncertainty to estimate a throughput of the R&D pipeline capacity. Here a mixed integer linear programming model based on discrete time representation was developed and a fixed sequence of tasks was addressed. However it could not handle a continuous time domain.

Jain and Grossman (1999) addressed the problem of scheduling the testing tasks for a fixed and predetermined portfolio of projects with resource constraints and task uncertainty. Two MILP models that perform the sequencing and scheduling of testing tasks for new product development under resource constraint were presented in this paper. The option for out sourcing at a higher cost was included in the model for the first time. All three of the approaches above use deterministic mathematical approaches. Blau *et al.* (2000) presented a simulation network model for risk management in the new product development process. Technical success factors and the degree of difficulty to accommodate the resource constraint were used to plot a graph of mean reward/risk ratio versus the probability of success to compare different candidates. The simulation model presented was designed to carry out tasks as fast as possible and provide the management an insight into the new product development portfolio, for example to show where resource constraints occur.

Subramanian *et al.* (2000) developed a computational architecture 'simulation-optimisation' to address uncertainty issues by combining discrete event stochastic simulation and deterministic optimisation. The R&D pipeline management problem was viewed as the control problem of a performance-oriented resource constrained, stochastic, discrete event, and dynamic system. The model has two modules. The simulation module simulates and the optimiser module solves mathematical problems and makes decisions. Initially a portfolio is built by solving a resource over booked optimisation program similar to that of Honkomp (1998). Then three types of regulatory and supervisory control are used to solve the initially prepared portfolio.

The focus of the above literature, however, is the new product development process, and not the design and planning of manufacturing facilities. Decisions regarding manufacturing of material are of importance as it will affect the time to market and the market share captured by the new drug. In most of the literature it is assumed, for instance, that there are no capacity limitations, or that the production levels of other products do not affect the production level of a new product. Rotstein *et al.* (1999) considered the problem where the manufacturing capacities for three products that are in clinical trials are to be determined. The authors used a scenario tree to capture the outcomes of the clinical trials.

Papageorgiou *et al.* (2001) describe an optimisation-based approach to selecting both a capacity planning and investment strategy in the pharmaceutical industry. The problem is formulated as a MILP model, takes into consideration the scale-up, qualification and product lifetime in getting to the market, and includes a campaign planning strategy with a portfolio or products that are at different stages of development. As the resulting model size is prohibitively large, the authors suggest that alternative solution approaches are investigated. However even this model does not take into consideration the task of performing clinical trials in biopharmaceutical development and is a deterministic model only.

Grossman and Maravelias (2003) proposed a MILP model that addresses three issues: the handling of resource allocation as a decision variable; handling of cost and duration of tests as functions of the type, and, the amount of resources assigned to each test and the installation of new resources during the course of testing. The authors state that allocating more resources to some testing can reduce time and allows more flexible schedules to be constructed. This model is closer to the real world more than the previous ones

Grossman and Maravelias (2001) studied the simultaneous optimization of resource-constrained scheduling of testing tasks in new product development, and design/planning of batch manufacturing facilities. Their model is a large scale MILP that predicts from a portfolio of new products, which products should be tested, the detailed testing schedule, design decisions for the process network and production profiles of new and existing products. It is assumed that the costs, durations and chances of success are known for each test. Indeed this assumption is made for all the methods reviewed so far. Further, in all of the above literature little or no attention is paid to the market uncertainty with more emphasis being placed on technical uncertainty. The financial metric used as a measure of profitability in all the above methods is the net present value (NPV).

Gatica *et al.* (2003) presented a mixed integer linear programming method for capacity planning under uncertainty for the pharmaceutical industry in which the optimisation based approach selects the final product portfolio and the production planning and investment strategy simultaneously subject to the uncertainty of the

outcomes of the clinical trials for each potential drug. Levis and Papageorgiou (2004) outlined a mathematical approach programming approach for long-term, multi-site capacity planning under uncertainty in the pharmaceutical industry. Here the approach used was to select the optimum portfolio from a given set of candidates and planning of the manufacturing schedules under constraints.

Maravelias and Grossman (2004) proposed a mixed integer linear programming model for scheduling of tests for pharmaceuticals and agrochemicals. The model takes into account the uncertainty of the resources available and the demand on the resources by the tests.

1.4.7 Real options method

Rogers *et al.* (2002) presented a novel method where a stochastic optimisation model (OptFolio) of pharmaceutical research and development portfolio management using a real options valuation instead of the NPV approach as the financial indicator for making optimal project selection decisions. This paper takes into consideration the market uncertainties brought about by the fluctuations in demand and competition. This is an analogue of the Black-Scholes (1973) options pricing method and was first suggested by Myers (1984) when he classified research and development investment opportunities as real options best captured with the options analysis.

The stochastic framework suggested by Rogers *et al.* (2002) provides a road map for future decisions by making decisions of abandonment over time and calculating the minimum market value above which the development is continued under changing resource constraints. In a following paper Rogers *et al.* (2003) applied a Monte Carlo simulation procedure to the OptFolio model. This framework provided a sensitivity analysis of candidate drug valuations and a risk management analysis for balancing risk versus reward tradeoffs. The next section of the chapter provides a review of the modelling and simulation of biopharmaceutical drug development activities.

1.5 MODELLING AND SIMULATING BIOPHARMCEUTICAL DRUG DEVELOPMENT

1.5.1 CHALLENGES OF MODELLING THE DRUG DEVELOPMENT PROCESS

Simulation technology is used to understand complex systems and products prior to these ideas being prototyped, scaled up and put into full production (Johnson, 1998). Usefulness of models has been demonstrated in describing, designing and analysing systems (Banks, 1998).When modelling biopharmaceutical drug development the challenge is to model effectively the many different activities involved in taking a drug through the phases of drug development, which increase in complexity and duration as the drug approaches market launch. The company-and drug-specific business and process characteristics all have to be captured successfully and the resulting model should be able to evaluate operational and financial metrics such as the time-to-market, cost, revenue and the risk, which all feature in the decision-making process in drug development. The business process models have to be combined successfully with the models of the drug development activities. The pharmaceutical industry is far behind other industries in examining the usefulness of simulation technology for its R&D process (Johnson, 1998).

Bank (1998) points out that modelling a complex, large-scale system is usually more difficult than modelling a strictly physical system for one or more of the following reasons:

1. Few fundamental laws are available
2. Many procedural elements are involved which are difficult to describe and represent
3. Policy inputs are required which are hard to quantify
4. Random components are significant elements
5. Human decision-making is an integral part of such systems.

A model of the drug development process could be described as a discrete, dynamic and stochastic one. Discrete event simulation concerns the modelling of a system as it evolves over time by a representation in which the state variables change instantaneously at separate points in time (Law and Kelton, 1991). The system state is updated at each event, along with capturing and freeing of resources that may occur at that time. Given the high level of uncertainty inherent in the drug development process, point estimations made for simulations would not be useful in

decision-making. Therefore suitable distributions have to be assigned for the inputs in any model of the drug development process. Industrial collaboration would be required in the process of modelling the drug development activities, as realistic inputs in the form of assumptions and distributions would have to come from industrial experts.

Modelling has been applied in the field of bio processing in many ways. The mathematical modelling carried out for portfolio management in the pharmaceutical industry was discussed in Section 1.4. Luehrman (1994) describes a model configured to assess the risks and returns of new projects in the pharmaceutical industry using an options analysis approach with Monte Carlo simulations. Myers and Howe (1997) presented a life cycle financial model of pharmaceutical R&D. The authors present the estimates of the cost of capital based on analysis of the risk characteristics of pharmaceuticals and biotech stocks. Their approach was to investigate the different financial characteristics of the drug development process such as cost of capital and financial ratios of pharmaceutical companies.

Karri *et al.* (2001) presented a hierarchical framework to assist decision-making in the biopharmaceutical industry which considered the effect of planning of process development and allocation of resources to the overall value of the project. Stonebraker (2002) presented a model of a single project aimed at evaluating its commercial worthiness. This model took the different tasks of drug development into consideration. These included process development, manufacture, clinical trials and marketing, but the model was limited to the assessment of a single project. The power of modelling and simulation is not just in simulating potential outcomes, but also in allowing one to examine the impacts of the assumptions that inherently exist in the clinical development stage.

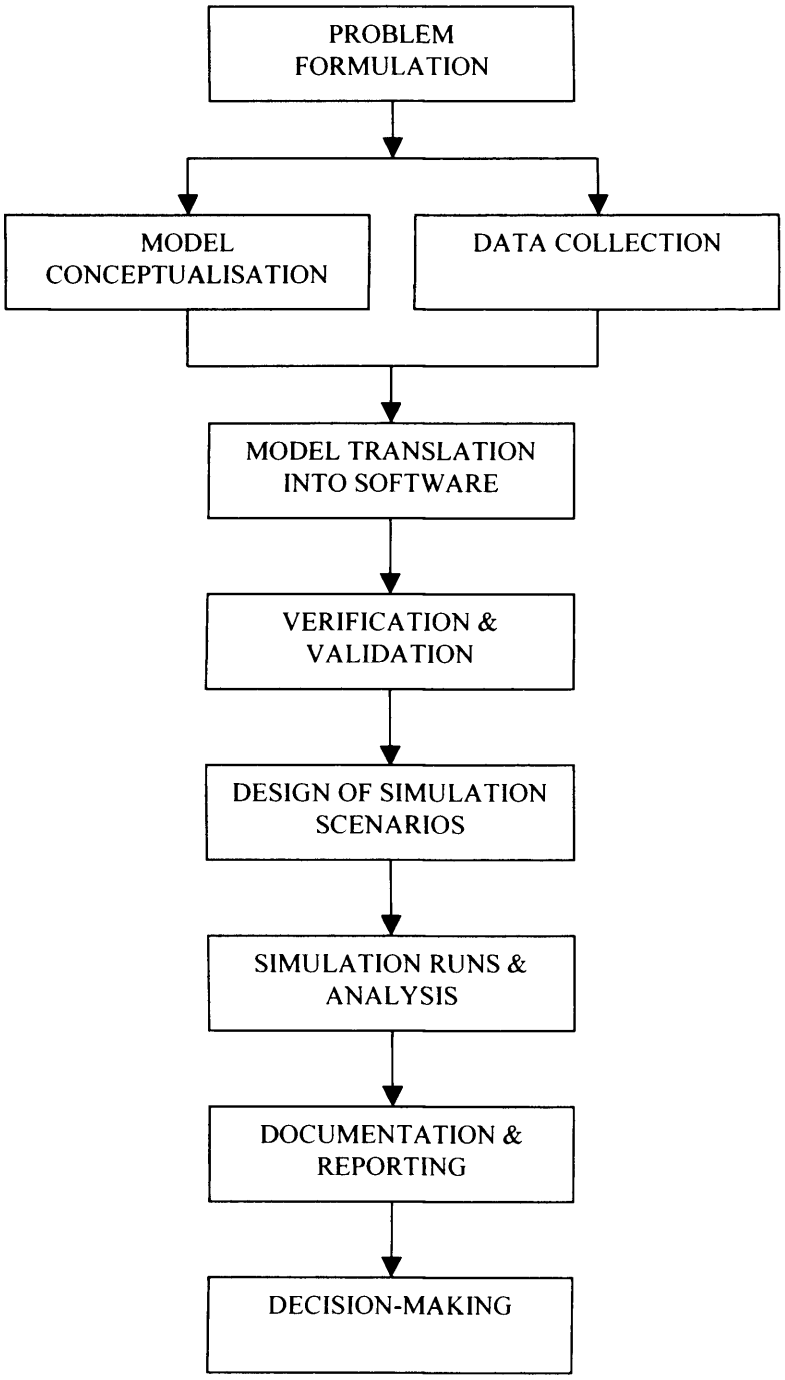


Figure 1.1 Steps in a simulation study (adapted from Banks, 1998).

Process modelling has traditionally been carried out for manufacturing operations, attempting to characterise mathematically the performance of unit operations in a manufacturing process. Coates and Kuhl (2003) describes the use of simulation software to solve engineering economy problems using three different examples. Gritsis and Titchener-Hooker (1989) demonstrated the use of SPEEDUP to model a train of three downstream unit operations, namely ultra filtration, precipitation and centrifugation so as to determine the minimum processing time. Petrides (1994) published a report that described the architecture and the important features of BioPro Designer, a bioprocess tool.

Zhou *et al.* (1997) illustrated the use of simulations in exploring the nature of and the impact of interactions that exist in a typical bioprocess for the recovery of an intracellular protein. Rouf *et al.* (2001a) demonstrated the use of two bioprocess simulators, Aspen BPS^{TM} and SuperPro Designer^{TM}, to simulate and compare the economics of using serum and serum-free medium for the production of tissue plasminogen activator (t-PA) from Chinese hamster ovary cells. Rouf *et al.* (2001b) reported a case study of using Bioprocess Simulator (Aspen Technology Inc., Cambridge, Massachusetts, USA) to study the economics of fed-batch operation. Bioprocess modelling has been used to explore different process routes from both a process and a business perspective with much success (Farid *et al.*, 2001; Mustafa *et al.*, 2004; Lim *et al.*, 2004). Shanklin *et al.* (2001) evaluates two commercially available software packages (Aspen Batch Plus v1.2, Aspen Technology, Inc., Cambridge, Massachusetts and Intelligent SuperPro v3.0, INTELLIGEN, INC., Scotch Plains, New Jersey) for modelling industrial biotechnology processes. Novais *et al.* (2001) presented a costing model used for economic comparison between conventional and disposable-based technology for the production of biopharmaceuticals.

Thomas (2003) discussed a design approach to biotech process simulations, with step by step descriptions and the challenges of such simulation projects. Most importantly the author emphasises that no specialist knowledge is needed for the development of simulations of bioprocesses and can be carried out by anyone who is computer literate. Baker and Wheelwright (2004) describe a financially based model of recovery process alternatives in biopharmaceutical manufacturing with a case study.

The authors conclude that having an empirical model to assess the financial impact of process improvement alternatives provides a clear basis for comparison and hence aid decision-making.

1.6 Risk analysis

Risk is defined as the adverse consequences of exposure to uncertainty (Blau *et al.*, 2000). The trade-off between risk and reward has been the basis of virtually every investment decision (Stambaugh, 1996). Decisions made during the drug development process are made in an uncertain environment characterised by technical and market-related risks. For example, common uncertainties in drug development include costs, development lengths, the efficacy and toxicity of the drug as well as patient population and drug price (Stonebraker, 2002).

Various approaches for identifying and measuring the uncertainty associated with a project appraisal have been advocated in the literature. The simplest method is to conduct a sensitivity analysis of each of the principle variables; the impact of $\pm x\%$ changes in each variable on the key output measures is observed. This provides a result for a given change, but it does not consider the likelihood of this change occurring (Farid, 2001).

High-risk environments often require the need to understand better the possible range of outcomes and simulation modelling is an attempt to understand the range of possible outcomes from a given situation (Doctor *et al.*, 2001). In Monte Carlo simulations, probability distributions are used as inputs in order to determine the probability distributions for the outputs. Through this method values will be found most frequently near the most likely outcome and less frequently for values further removed from that value. As a result, Monte Carlo simulation analysis has become established as a financial tool to help in risk analysis, particularly in investment decision-making (Doctor *et al.*, 2001). The use of Monte Carlo simulation is highlighted in the literature (Blau *et al.*, 2000; Brastow and Rice, 2003; Farid *et al.*, 2001). In addition commercial software packages for Monte Carlo simulation have been introduced that are relatively easy to use and inexpensive; examples include the spreadsheet add-ons @RISK (Palisade Corporation, Newfield, NY, USA) and Crystal Ball (Decisioneering, London, UK). Determining the probability distributions

of the key uncertain inputs is usually based on historical data or subjective estimates from industrial experts.

1.7 AIMS AND ORGANISATION OF THESIS

The preceding sections have provided a description of the uncertainty within the drug development process. The decision-making processes currently being applied in managing new product development has been reviewed. The current position of process and business simulation within the biopharmaceutical industry has also been highlighted. The literature survey highlights that at present no package allows both modelling the drug development process and effective decision-support that relates management decisions to the following strategic business issues: resource management, costing and risk.

The aim of this thesis is to investigate the possibility of capturing both the technical and business perspectives of the biopharmaceutical drug development process in a single and consistent framework. This can facilitate more informed decision-making when evaluating alternative management strategies for the drug development process and permit risk analysis. In order to achieve this aim a set of objectives was identified and forms the basis of each of the following chapters.

Chapter 2 presents an investigation of the drug development process, highlighting the different tasks that are involved in taking a drug candidate into the market. The process development, manufacture and the clinical trials are described in detail. The regulation process that is being applied to biopharmaceuticals is highlighted. The business of biopharmaceutical drug development is presented outlining the cost, time to market and the failure of drugs during the development process. This analysis helps to understand the risk and uncertainty inherent in the drug development process.

In Chapter 3, the conceptual framework and the implementation of the software tool is presented. The main characteristics of the biopharmaceutical drug development problem domain are identified early in the chapter, as well as the scope of the modelling effort. The approach taken to represent the key activities in a drug development process is introduced. Its key features and parameters that satisfy both

drug development task and business applications are discussed. The implementation of the conceptual framework into a simulation-based decision tool for modelling the drug development process is then described.

Chapter 4 discusses the use of the tool to model the drug development process. The different applications the tool could be used for are introduced at the beginning of the chapter. This is followed by a discussion on the simulation process and the key decision points in the model. Graphical user interfaces are presented to familiarise the user with the tool. Next, the key inputs and outputs of the simulation tool are identified. Finally, the data collected as default values for the simulation are presented along with the assumptions made.

The application of the tool to model the drug development process and compute cost of development and time to market are presented in Chapter 5. A sensitivity analysis to identify the key parameters in drug development is carried out next. A hypothetical case study is set up to assess three different strategies for manufacturing material during the clinical trials and for the market. The Monte Carlo simulation technique is used to highlight the benefits of incorporating technical and market-related uncertainties when evaluating development strategies.

In Chapter 6, the simulation tool developed is applied to select a portfolio of drugs under different levels of resources. Again a hypothetical case study is used in which different project portfolios are generated by the tool for different resource levels. Next, the reward and risk values for the different portfolios are calculated. An efficient frontier is then constructed for the different resource levels to select the most optimum portfolio.

Chapter 7 provides a summary of the main contribution of this work and provides suggestions for future work. The extra data that was used for the case study in Chapter 6 is presented in Appendix A and a paper by the author, published through the course of this work, is attached in Appendix B.

CHAPTER 2

BIOPHARMACEUTICAL DRUG DEVELOPMENT

2.1 INTRODUCTION

The pharmaceutical industry can be defined as a complex of processes, operations, and organisations involved in the discovery, development and manufacture of drugs and medications (Shah, 2004). Biologically-derived compounds can be produced efficiently, are generally more specific in their action and provide an alternative method of treatment to chemically-derived compounds. The biotechnology industry is in the growth phase of its industry cycle and this phase will be marked by rapid sales growth due to a bevy of new products entering the market place over the next several years (Ginsberg *et al.*, 2002). In 2002 there were over 350 biotechnology medicines in development in the US by 144 companies and the National Cancer Institute for nearly 200 diseases (Holmer, 2002; Burrill and Company, 2004a). These include 178 medicines for cancer, 47 for infectious diseases, 26 for autoimmune diseases and 21 for AIDS/HIV and related conditions (Holmer, 2002). Greener (2001) includes the discovery stage and states that there are almost 1200 biotech products in different stages of development.

The impressive financial rewards that can be reaped by a company by successfully bringing a biopharmaceutical product to the market have led to tremendous pressure to reduce time to market for products in the development pipeline. The world market for protein drugs was estimated at US$ 41 billion at the end of 2002 (Ernest and Young, 2003). However launching these products into the market is costly, risky and time consuming. On average it takes over 12 years to bring in a new pharmaceutical product to the market (Burrill and Company, 2004b). Worldwide there were 600 publicly traded biotech companies in 2002, which made a combined loss of more than US$ 12 billion (Ernst and Young, 2004).

This chapter initially provides a general introduction to biopharmaceuticals and their application as therapeutics in Section 2.2. In Section 2.3 the tasks, costs and risks of biopharmaceutical drug development are investigated and the economics of biopharmaceuticals in the marketplace are highlighted in Section 2.4. Finally the future of drug development is discussed in Section 2.5. The chapter ends with a summary of the findings.

2.2 BIOPHARMACEUTICALS

Until recently, the vast majority of biopharmaceutical products were protein based (Table 2.1). However, during the 1990s, nucleic acid-based biopharmaceuticals also come to prominence, being employed in gene therapy and antisense technology (Walsh, 1998). Biological therapeutic products generally refer to any virus, protein, therapeutic serum, vaccine, blood component or gene transfer product destined for therapy. An understanding at the molecular level of how the body functions in health and the deviations which characterise the development of disease often render potential strategies likely to cure or control that disease. This understanding is used as the base for the discovery of biopharmaceuticals. The cause of disease is normally due to the lack of a single regulatory molecule, usually a protein. Other deceases such as inflammation and cancer however could be due to many factors and are hence more complex to treat. Biopharmaceuticals differ from chemical-based drugs by the way they are produced as well as regulated. However in some instances, categorising pharmaceuticals as products of biotechnology or chemical synthesis becomes somewhat artificial. For example, certain semi-synthetic antibiotics are produced by chemical modification of natural antibiotics derived initially by fermentation technology (Walsh, 1998).

Table 2.1 Some protein types that are being used as therapeutics

Blood clotting factors	Monoclonal antibodies
Colony stimulating factors	Neurotrophic factors
Enzymes	Polypeptide anticoagulants
Growth factors	Polypeptide hormones
Interferons	Thrombolytic agents
Interleukins	Vaccines

2.3 BIOPHARMACEUTICAL DRUG DEVELOPMENT

Linkages between product and process technology differ substantially across the industries (Utterback, 1994). Pisano (1996) states that these differences influence the nature of both the technical and organisational challenges of process development. As an example, the author points out that in many types of assembled goods industries (automobiles, personal computers, consumer electronics), product functionality and features are not severely constrained or heavily impacted by the process design. At the other end of the spectrum are industries such as pharmaceuticals, chemicals, semiconductors, and advanced materials, where product and process designs are highly interdependent and changes in process technology can have a significant impact on product characteristics. Biopharmaceuticals and the process of manufacture clearly fit in this latter category.

In this section the many different complex activities involved in taking a biopharmaceutical drug candidate to the market from the point at which it has been identified as a potential therapeutic agent are described. The average process of drug development costs over US$ 400 million and takes an average 10 years (DiMasi *et al.*, 2003). In addition, the complexity of drug development and clinical testing procedures has increased significantly over the past years (Kleinberg and Wanke, 1995).

The first step involved in drug development would be the process of drug discovery, where thousands of molecules are screened for promising new therapies. Traditionally the knowledge of interactions at the molecular level, for regulatory proteins has been used to identify new drug candidates. Once these bio molecules have been identified and isolated, they are subjected to many trials and tests to ascertain efficacy and toxicity. In addition to these tests, a process to produce the drug in higher quantities has to be developed, tested and commissioned. These development activities are time-consuming, costly, and contain much uncertainty. An introduction to the regulatory activities involved is presented, followed by a description of the development process itself.

2.3.1 Regulation of drug development

One of the major hurdles to commercialisation is achieving regulatory approval for the drug as well as of the manufacturing process (Humphrey, 1996). The process of drug development is closely scrutinised by regulatory authorities in every country. In the United Kingdom, it is the Medicines and Healthcare products Regulatory Agency (MHRA, http://www.mhra.gov.uk/). The European Union region is regulated as a whole by the European Agency for the Evaluation of Medicinal Products (EMEA, http://www.emea.eu.int/). Quality (drug stability; drug substance; dosage form), safety (single and repeated dose toxicity; short and long term toxicity; carcinogenicity; reproductive toxicology) and efficacy (therapeutical activity; clinical safety; dose/response trials; good clinical practice) remain the three basic criteria for the evaluation of the medicinal products by the EMEA (Benzi and Ceci, 1998). In addition the same authors describe how the value of the drug, measured by the quality of life added to the patients and the economic outcomes within the social health service are considered when assessing a drug for approval within the European Union. Walsh (2003) provides a description of the approval procedure deployed by the EMEA and presents a description of all the biopharmaceuticals approved in the European Union, which amount to some 88 products.

The foremost regulatory authority for medicinal products in the world is the United States Food and Drug Administration (FDA, http://www.fda.gov/). The Centre for Drug Evaluations and Research (CDER) and the Centre for Biologics Evaluation and Research (CBER), as part of the FDA, oversee the development and marketing approval process of new biopharmaceuticals. The major responsibilities of the FDA with regard to drugs include the following (Walsh, 1998):

- Assess pre-clinical data and decide if a potential drug is safe enough to allow commencement of clinical trials in humans
- Protect the interests and rights of patients participating in clinical trials
- Assess pre-clinical and clinical trial data generated by a drug and decide if that drug should be made available for general medical use (i.e. if it should be granted a marketing licence)
- Oversee the manufacture of safe effective drugs (inspect and approve drug-manufacturing facilities on the basis of compliance with the principles of good manufacturing practise as applied to pharmaceuticals)

- Ensure the safety of the US blood supply

For most of this chapter the standards and statistics followed will be that of the FDA. The drug development process will now be described.

2.3.2. Drug development pathway

The progress of a candidate through the many tests and other development activities is recognised as the drug development process. Figure 2.1 illustrates the drug development pathway.

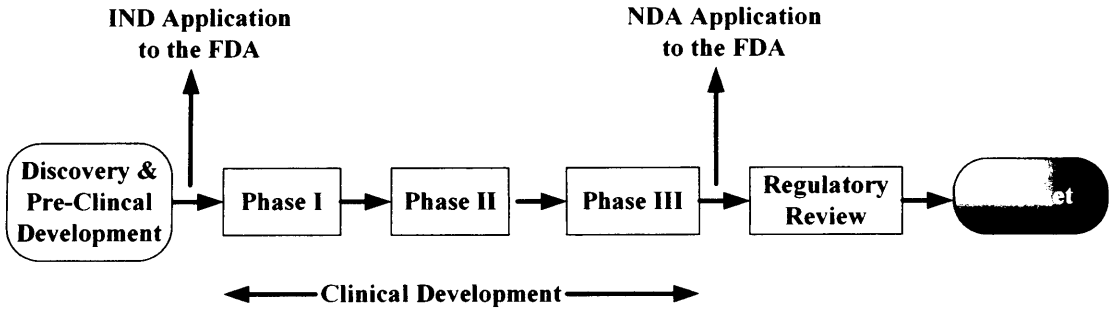


Figure 2.1 A schematic representation of the drug development pathway.

Only about 1 in 10,000 molecules that enter the drug discovery phase will finally make it to the market (Carr, 1998). In parallel to the clinical trials, process development and manufacturing of the material in increasing quantities has to be addressed. The discovery stage of drug development is described next.

2.3.2.1 Drug discovery

The discovery of biopharmaceuticals can be attributed to the logical application of our ever increasing knowledge of the biochemical basis of how the body functions. In a simplified sense diseases are caused by the lack of a particular regulatory molecule, which is mostly a protein. Identifying this molecule is the first step in drug discovery. However, the knowledge of this regulatory molecule does not automatically translate into an effective therapeutic agent. The physiological responses displayed by a molecule *in vitro* or an animal model may not accurately predict the physiological responses seen when the product is administered to a human. For example, many of the most promising biopharmaceutical therapeutic agents (e.g. virtually all the cytokines) display multiple activities on different cell

populations (Walsh, 1998). The availability of super-computers has spurred the growth of structure based or rational drug design, whereby drugs can be designed by analysing the structure of the molecular target and its active site (Figure 2.2).

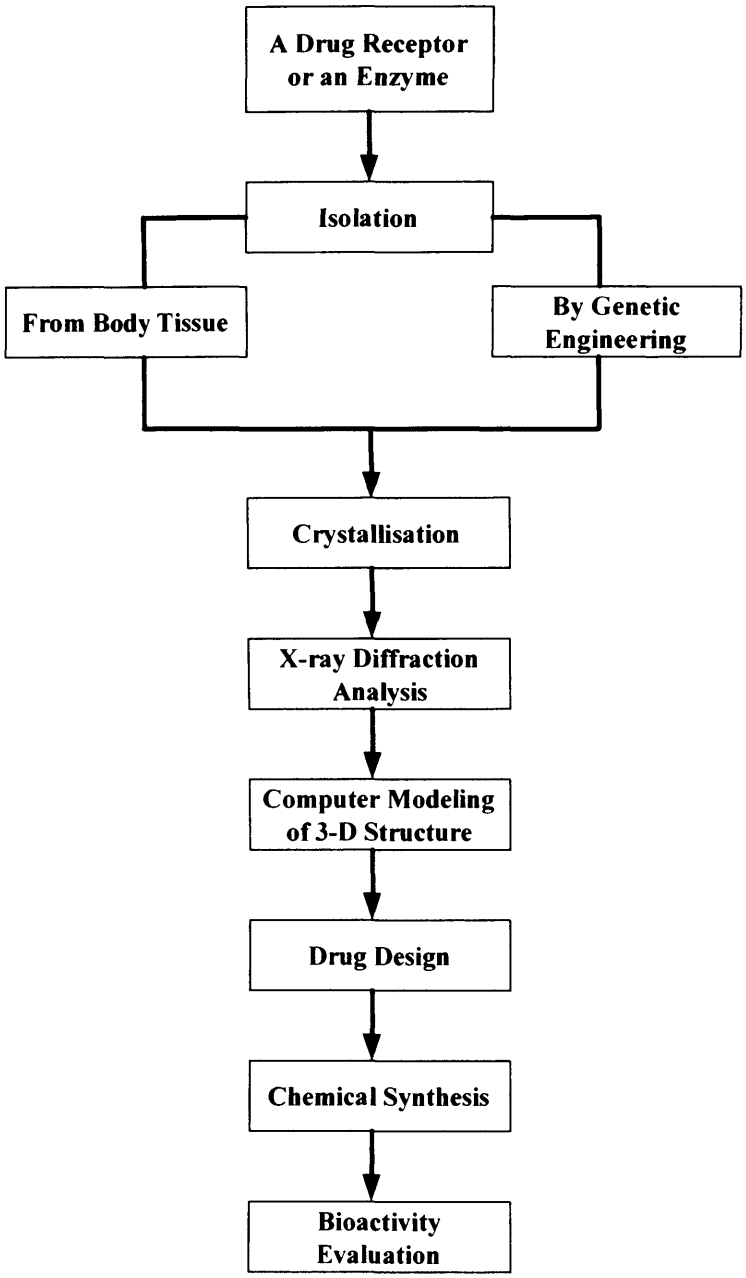


Figure 2.2 Steps involved in using structure-based (rational) drug design to test and develop drugs based on drug-receptor interactions (Clemento, 1999).

Structure-based strategies that integrate the techniques of X-ray crystallography, computational chemistry and nuclear magnetic resonance spectroscopy to design drugs atom by atom are slowly replacing more traditional methods such as random screening and structural modification of existing compounds (Clemento, 1999).

Gardner *et al.* (2004) describes the application of novel high throughput physical-chemical technologies to the pharmaceutical discovery and development process.

All the rationale drug design methods were designed for chemical entities and therefore the integration of biological data with chemical information poses a unique challenge to the biopharmaceutical industry (Shi *et al.*, 2003). Bioinformatics refers to biological information, traditionally the sequence information on large molecules such as DNA, RNA and proteins. Chemoinformatics on the other hand deals with chemical information of small molecules drug. Biochemoinformatics is a new term being used to describe the research needs arising by the integration of bioinformatics and chemoinformatics (Shi *et al.*, 2003). A comparison of the chemoinformatics and the bioinformatics is presented in Table 2.2.

Table 2.2 Biochemoinformatics: integrating bioinformatics with chemoinformatics (Shi *et al.*, 2003)

Bioinformatics (Gene/RNA/Protein)	**Chemoinformatics (Compound)**
Sequence (ATGC and so on)	Structure (for example SMILES)
2D structure and motif	Molecular connectivity (for example SDfile)
Active binding site	Pharmacophore
Sequence homology	Structure similarity
Pylogenic tree	Molecular similarity and diversity
Gene ontology	Chemical property
Gene function	HTS and activity fingerprint
Target identification and validation	Lead identification
Micro array gene expression profiling	Combinatorial library design and synthesis
Regulatory network	Metabolic profile

2.3.2.2 Pre-clinical phase

The physicochemical and other properties of any newly identified drug candidate have to be characterised in detail prior to clinical trials. The focus at this stage is on maximising the chance of identifying an ultimately unsuccessful biotechnology product as early as possible in the drug development pathway. A prerequisite to such a characterisation is initial purification of the protein to homogeneity, which normally requires a combination of three or more high-resolution chromatographic steps. This purification protocol is designed with great care as it usually forms the basis of subsequent pilot and process scale purification systems. The purified product is then subject to a range of tests that are aimed at characterising it fully. Once these characteristics have been defined, they form part of the basis of quality control (QC) identity tests routinely performed on the product during commercial manufacture.

Regulatory authority to commence clinical trials in humans is subject to successful pharmacological and toxicological tests being carried out on animals. Such pre-clinical studies can take three years to complete and cost from $2 million to $30 million (Walsh, 1998). Safety evaluation in acute studies would normally include two different animal species and for chronic toxicity, one species can be sufficient if the two species initially studied have comparable toxicity profiles (Febbraro, 2002). The range of major tests undertaken on a potential new drug candidate during the pre-clinical phase are (Walsh, 1998):

- Pharmacokinetic profile
- Pharmacodynamic profile
- Bioequivalence and bioavailability
- Acute toxicity
- Chronic toxicity
- Reproductive toxicity and teratogenicity
- Mutagenicity
- Carcinogenicity
- Immunotoxicity
- Local tolerance

The above tests are used to identify any effect on major systems like the cardiovascular, respiratory, renal and central nervous systems. The exact range of tests that regulatory authorities suggest should be undertaken for biopharmaceutical substances remains flexible (Walsh, 1998). Normally only a subgroup of the standard tests for chemical-based drugs is considered appropriate. In addition tests for mutagenicity and carcinogenicity are not likely required for most biopharmaceutical substances. The drug is normally patented by the developing company once it has been characterised and perhaps early clinical work is under way in order to ensure it receives maximal commercial benefit from the discovery (Walsh, 1998). If the pre-clinical testing yields favourable results and the developers are confident about the therapeutic and economical value of the drug candidate, it is taken into the clinical development phase. This is described next.

2.3.2.3 Clinical trials

The clinical trials are the most expensive and lengthiest process of the drug development pathway. The trials are conducted in increasing size and complexity to first determine the toxicity, dosage and then the efficacy in humans. In order to get approval to market the product, the company has to convince the regulators that it is safe and has a higher efficacy than current therapies in use. Satisfying these broad aims usually requires an ordered program of clinical trials, each with its own specific objectives. To conduct clinical testing in the United States, a manufacturer must first file an investigational new drug application (IND) with the FDA. Once drug developers believe that they have enough data gathered of safety and efficacy, they will compile the results of their tests in an application to regulatory authorities for approval. In the United States, manufacturers submit a biological license application (BLA) to the FDA for review and approval.

a) Phase I clinical trials

The Phase I clinical trials are conducted in healthy humans to confirm the safety of the new drug candidate and to gather information regarding absorption, distribution, metabolic effects and excretion. Approximately 20 – 30 healthy volunteers are recruited for the first phase trials. The results from Phase I trials are used to design well-controlled, scientifically valid Phase II trials. Material for Phase I are manufactured in a lab or a multi purpose pilot plant.

b) Phase II clinical trials

The Phase II trials are conducted in 200 – 300 subjects who have the targeted disease or condition and are designed to further assess the common short-term side effects of the drug and establish preliminary data on efficacy. This normally takes up to two years. Phase II material is made either in a multi purpose pilot plant or in a small pilot plant.

c) Phase III clinical trials

The final phase of clinical trials is used to firmly establish the efficacy and uncover side effects that occur infrequently. Several thousand patients are used at this stage with many centres being used and the results are used as an adequate basis for extrapolating the results to the general population and as information in the product label. The Phase III trials can take up to three years in duration. Here, an acceptable level of efficacy is defined before the commencement of the trial. This has to be done, as the drug may not have its desired therapeutic effect on all the patients. For example it may be decided that the drug has to be efficacious in 25% of the patients, so as to be judged efficient. Therefore if the observed incidence is below this set minimum, the trials can be terminated with the drug being judged unsuccessful

d) Post marketing surveillance

Finally, post-marketing safety surveillance is carried out to assess the long-term effects of drug and could result in drugs being taken out of the market. Immune Globulin Intravenous (Human), Gammar-P I.V., 10 gm (Aventis Behring L.L.C) was recalled by the FDA in April 2004 (http://www.fda.gov/cber/recalls). Approximately 10 biological products are recalled every year by the FDA. Parker and Lahr (1999) cite the increasing complexity of product design, manufacturing process, product liability and the stringent regulation process as a reason for the recall of drugs. The authors explore different recall strategies and outline steps by which a firm can minimise damage due to a recall.

With clinical trials being the longest stage of the drug development process, many suggestions have been made on how the efficiency of the clinical trials can be improved (Marks and Power, 2002; Norris, 2001). The authors suggest the use of information technology for the recruitment process and data mining for uncovering

patterns or systematic relationships between large amounts of data. To conclude a summary of the description of the clinical trials is presented in Table 2.3.

Table 2.3 Summary of clinical trials

Trial Phase	Evaluation undertaken and usual number of patients	Average duration (years)
Phase I	Safety testing in healthy human volunteers (20-80)	1
Phase II	Efficacy and safety testing in a small number of patients (100-300)	2
Phase III	Large-scale efficacy and safety testing in substantial numbers of patients (1000-3000)	3
Phase IV	Post-marketing safety surveillance undertaken for some drugs which are administered over a particularly long periods of time (number of patients vary)	Several years

2.3.2.4. Process design and product development

Once the clinical development of a drug candidate commences, the product and process development work has to be pursued. The most efficacious and safest drug will not bring in revenue until the process to manufacture it is developed and approved. The product development concerns the characterisation as described in Section 2.2 and the formulation work. A suitable process to manufacture the material for the clinical trials and the market has to be developed on time. The cost of developing and implementing new process technology often approach and sometimes greatly exceed the cost of product development (Pisano and Wheelwright, 1995). Bioprocess development is essentially a multi-disciplinary task involving microbiology, biochemical engineering, biochemistry, virology, and molecular biology.

The regulations demand that the process used to manufacture the material for the Phase III clinical trials has to be subsequently used for the manufacture of the material for the market. Therefore the manufacturing process has to be developed by the beginning of the Phase III clinical trials. In biotechnology, new molecules are so

complex to manufacture that developing basic process technology often determines the lead times for commencing human clinical testing. In addition, low-yielding processes often make it impossible for a company to produce enough material to supply all the necessary clinical trials in a timely fashion and can lead to delaying the clinical trials and the commercial launch of the product. Innovative process technologies are an under-exploited way for organisations to protect and extend the proprietary position of their product (Pisano and Wheelwright, 1995). A summary of the different activities involved in process development and the key outcomes are summarised in Table 2.4.

Table 2.4 Key activities and outcomes involved in bioprocess development (adapted from a presentation at a MBI course at University College London by Hari Pujar, Merck)

Process development activities	**Key outcomes**
Designing process conceptually	Integrates fermentation,
Developing key analytical assays	purification and assay
Developing process at lab scale	development
Process science	Supplying bulks for downstream
Engineering scale-up	development
Determining process sensitivities	Manufacture of clinical supplies
Process intensification	Documentation for each transfer
Specifying equipment requirements	Factory start-up
Defining manufacturing operating conditions	Product licensure
Defining process validation parameters	

Process engineers have long recognised that when a project is started at the laboratory scale, industrial systems must also be considered. The high importance of process development has resulted in novel methods being pursued to reduce the time to market of biopharmaceuticals (Titchener-Hooker *et al.*, 2001). With gains in the efficiency in electronic data management, the clinical trials are speeding up, increasing the pressure on the process development work (Norris, 2001). The same author states that having a clear business-process development definition, a multi-functional project team and the deployment of information technology solutions (e.g.

simulation) as key areas to that need to be addressed in order to avoid delays due to process development.

Table 2.5 Methods of reducing bioprocess development times and increasing process quality (Titchener-Hooker *et al.*, 2001)

Ultra scale-down to examine key bioprocess parameters
Systematic bioprocess selection including use of accumulated knowledge
Bioprocess modelling to complement scale-down and check design options
Scale-down of whole bioprocess for per-pilot process guidance
Analytical information in real-time to achieve addressable bioprocessing
Bioprocess decisional tools to enable the consequences of both business and process choices on project success to be assessed

2.3.2.5 Product manufacture

Once sufficient yields have been achieved through the process development work, the manufacturing of materials takes place. The transfer of new biotechnological processes from research and development to manufacturing is always fraught with difficulties (Gerson *et al.*, 1998). The authors state that increased success in the transfer of new processes from development to manufacturing can markedly increase the number of new drugs and vaccines brought to market, reduce the time to market and increase the profitable lifetime of the product. The uncertainty surrounding product approvals, the long lead times and the high cost of getting a facility functional have made biopharmaceutical manufacture a formidably challenging task (Brastow and Rice, 2003). Biologics are manufactured from biological sources such as mammalian-derived cells or bacterial hosts in a process that is much more expensive, complex and time consuming than the manufacture of chemical compounds. Typically the cost of goods varies from US$ 500 – 5000 per gram (personal communication, Richard Francis, Protherics, London, UK). Enbrel (Amgen, California, USA) and Herceptin (Genentech, USA) have sales values in excess of US$ 4000 per gram (Curling, 2000).

The manufacture of biopharmaceuticals is a highly regulated and rigorously controlled process. In order to gain a licence for the manufacture of material, the sponsoring company must demonstrate to the regulatory authority that not only is the

product itself is safe and effective, but that all aspects of the proposed manufacturing process comply with the highest safety and quality standards. The principles underlining such standards are summarised in publications, which detail good manufacturing practices (GMP). Muller *et al.* (1996) provides an overview of regulations with special regards to GMP of biopharmaceuticals in different countries. The authors discuss the regulatory procedures with regard to each different stage of manufacturing.

Biopharmaceutical manufacture comprises the upstream process of protein expression and the downstream process of purification. A typical campaign for a single batch in a mammalian cell based process would last 7 – 8 weeks, with shorter time periods for products derived from Ecoli or yeast fermentation. Biologicals are distinguishable from their chemically synthesised counterparts with respect to their manufacturing process and the impact on the product quality and safety. The quality of biologicals is defined by the chosen production and manufacturing process. Minor changes in the manufacturing process can affect the quality of the drug. Regulations demand that depending on the complexity of the change to the manufacturing process such alterations have to be followed up with new clinical trials or pharmacokinetic studies, to prove the consistency of the product. Delays in the time to market are often due to deficiencies in manufacturing rather than to the scientific or clinical sections in the biotechnology industry (Fisher & Pascucci, 1996).

Since changes to the FDA regulations in 1996, biological products can be produced at any facility and are not confined to a single licensed facility. Therefore purpose-built facilities do not have to be built prior to product approval and early commercial production can take place in a contract manufacturing facility. Such outsourcing to contract manufacturers has become increasingly popular with both large pharmaceutical companies and the biotech community in particular (Byrom, 2000) and is currently growing at a rate of 20% per year (Savage, 2000). In 2002, over 30% of the manufacturing capacity was held by contract manufacturing organisations (Ginsberg *et al.*, 2003).

Building a facility with a capacity of 100, 000 L could cost US$ 200 – 400 million and take up to 5 years to be fully operational (Ginsberg *et al.*, 2003). The issue of having manufacturing capacity to meet the demand of the new drugs coming into the market is an issue of much discussion within the industry today (Molowa, 2001; Molowa, 2002; Ginsberg *et al.*, 2003). In 2000 – 01 several sources reported that the biotechnology industry was suffering from a severe shortage of manufacturing capacity for recombinant protein therapeutics, especially monoclonal antibodies (e.g. Byrom, 2000; Molowa, 2001). However more recent reports suggest that manufacturing capacity will not become a bottleneck (Ginsberg *et al.*, 2003; Grimster, 2003; Sinclair, 2003). The manufacturing capacity in 2002 was estimated by Ginsberg *et al.* (2003) to be 413 000 litres worldwide.

In planning manufacturing capacity, estimates have to be made in advance about the demand in order to avoid losses due to not being able to meet the demand of the market. Given the number of products in clinical development and the growth of the market for the products currently in the market, it is projected that 940 000 litres of mammalian cell culture-based manufacturing will be needed by 2005/2006 (Ginsberg *et al.*, 2003). The ability to meet the above manufacturing demand will determine whether the new biopharmaceuticals that make it to the market will be able to justify their economic value. Ginsberg *et al.* (2003) provides a breakdown of the manufacturing capacity being added at different companies and using these values, concludes that the capacity to meet this demand in 2005 does exist (Tables 2.6 and 2.7).

Table 2.6 Current and forecasted biological manufacturing capacity (Ginsberg *et al.*, 2003)

Contractors	**Current volume (L)**	**Additional volume (L)**	**Total volume (L)**
Boehringer-Ingelheim	90,000	90,000	180,000
DSM Biologics/Catalytica	8,100		8,100
Lonza	14,500	43,500	58,000
Other	9,800		9,800
Contractors Subtotal	**122,400**	**133,500**	**255,900**
Drug/Biotech Companies			

Abbott/BASF/Knoll	3,500	48,000	51,500
Abgenix		32,000	32,000
Aventis	2,000	5,000	7,000
American Home Products/Immunex		100,000	100,000
Amgen	80,000	80,000	160,000
Avecia	9,000	3,000	12,000
Biogen	12,000	180,000	192,000
BioMarin	1,010		1,010
Bristol-Myers-Squibb	10,000		10,000
Chiron	10,000		10,000
Chugai Pharmaceuticals		15,000	15,000
Genentech	96,000	96,000	192,000
Genzyme	1,000	10,000	11,000
GlaxoSmithKline	5,000		5,000
Human Genome Sciences	2,000	40,000	42,000
ICOS	3,850		3,850
IDEC	2,000	90,000	92,000
Imclone		30,000	30,000
J&J/Centocor	10,000	20,000	30,000
Medarax	1,961	29,412	31,373
MedImmune	5,000		5,000
Protein Design Labs	750	22,000	22,750
Roche	20,000		20,000
Xoma	4,000	4,000	8,000
Other	12,000		12,000
Drug/Biotech subtotal	**291,071**	**804,412**	**1,095,483**
Total industry capacity	**413,471**	**937,912**	**1,351,383**

Table 2.7 Future monoclonal antibody manufacturing capacity requirement estimates (Ginsberg *et al.*, 2003)

	2000	**2005/2006**
Sales of antibodies on market (US$M)	2637	5304
New antibodies launched in 2001 - 2005		21
Average estimated sales of new antibodies (US$M)		300
Total new antibody sales (US$M)		6300
Total antibody sales (US$M)		11604
Estimated quantity sold (kg)	500	2200
Capacity required (l)	**98,039**	**431,415**
Sales of proteins on market (US$M)	10701	21523
New proteins launched in 2001 – 2005		19
Average estimated sales of new proteins		300
Total new protein sales		5700
Total proteins sales		27223
Estimated quantity sold (kg)	45	114
Capacity required (l)	**200,000**	**940,221**
Total required capacity (l)	**298,039**	**940,221**
Industry capacity (l) (Table 2.8)	**413,471**	**1,351,383**

Having described the different activities that make up the drug development process, the costs and risks involved will be discussed next.

2.4 BUSINESS OF BIOPHARMACEUTICAL DRUG DEVELOPMENT

As described in Section 2.4, the development of biopharmaceuticals is a lengthy and complex process that is both expensive and risky. The objective of this section is to discuss the time lengths and costs involved with drug development and to review the attempts made at quantifying the risk. The cost of bringing more complex drugs to market is increasing impacting both the drug development pipeline and return on investment for emerging and long established drug development companies (Foo *et al.*, 2001). In the year 2002, globally, biotechnology companies employed approximately 190 000 personnel and made a total revenue of over $41 billion (Ernst and Young, 2003).

2.4.1 Time to market

Time to market is a key driver in the business of drug development. For a product that is estimated at bringing in annual revenue of $350 million, about a $1 million is lost for each day it is delayed in entering the market. The development times for biopharmaceuticals have always been shorter than for classical chemical entities (Gosse *et al.*, 1996). The tremendous rewards available when a product is introduced to the market have added pressure on companies to shorten the time to market. Therefore the time to market remains a subject of much discussion and research within the pharmaceutical community.

Several studies have been undertaken to research the time to market of pharmaceuticals. DiMasi *et al.* (2003), in a detailed study of 68 randomly selected new drugs calculated the average time to market. The authors concluded that the average time to market (from start of clinical testing to market) was on average 90.3 months, which was less than the 98.9 months from a previous study by the same researchers (DiMasi *et al.*, 1991). However the majority of the drugs studied were new chemical entities and only 6 were biopharmaceuticals (4 recombinant proteins and 2 monoclonal antibodies). The reason for the shortening in the time has been attributed to the much shorter approval times in the mid to late 1990s that were associated with the implementation of the Prescription Drug Use Fee Act of 1992.

These accelerated process methods apply to drugs that are for life threatening diseases that do not have adequate therapies currently in use, for example AIDS and cancer. The European Medicine Evaluation Agency (EMEA) offers a centralised process whereby a new drug can obtain approval for market for the entire European Union through one application, but does not have a clearly defined class for products for faster review.

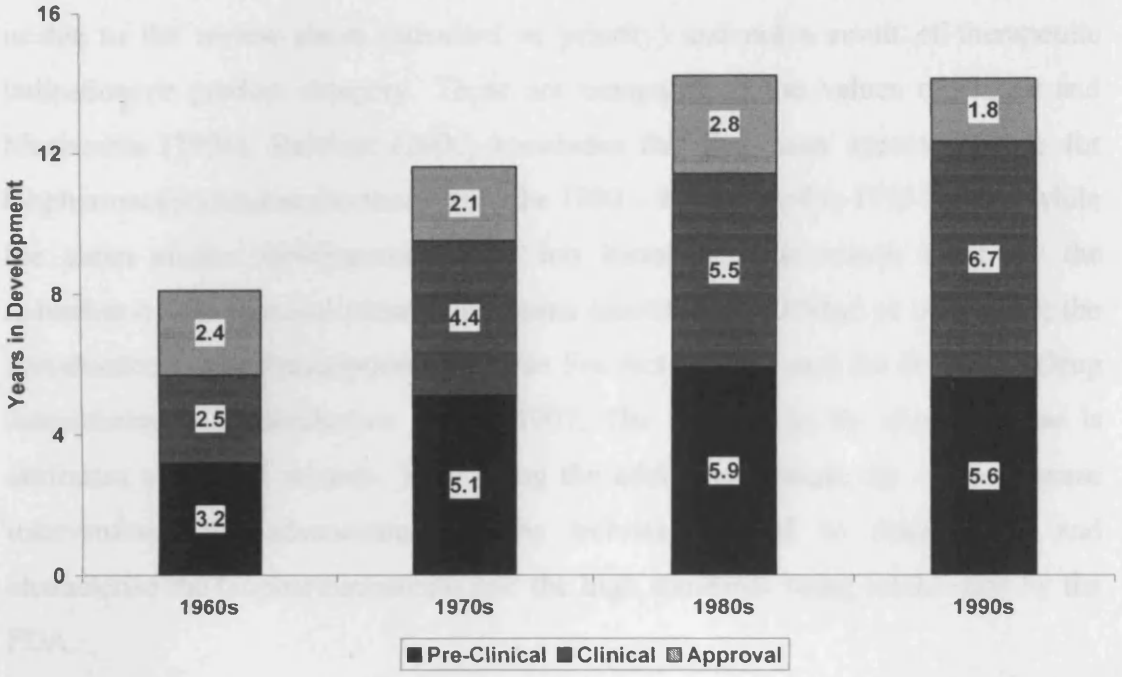


Figure 2.3 The change in development time for pharmaceuticals over the last four decades for the different activities. This shows that the durations have been on the increase (Burrill and Company 2004b).

Gosse and Manocchia (1996) provide the earliest record of time to market for biopharmaceuticals. The first 29 biopharmaceuticals approved in the US (1980-1994) were examined to breakdown the phase lengths of clinical and review stages. The average development time was calculated as 61 months and the average values for different therapeutic categories were presented. The authors conclude that the mean time for development for biological entities (61 months) is 38.9 months shorter than the mean development time for new chemical entities approved during the same time phase. The authors suggest two reasons for this observation. The first is that these compounds being biological entities, they have specific pharmacologic profiles and defined physiological mechanisms. The second reason is that this set of biological entities had recombinant proteins, which had purified non-recombinant protein counterparts in therapeutic use by the general population, therefore had clinical data available enabling faster clinical development.

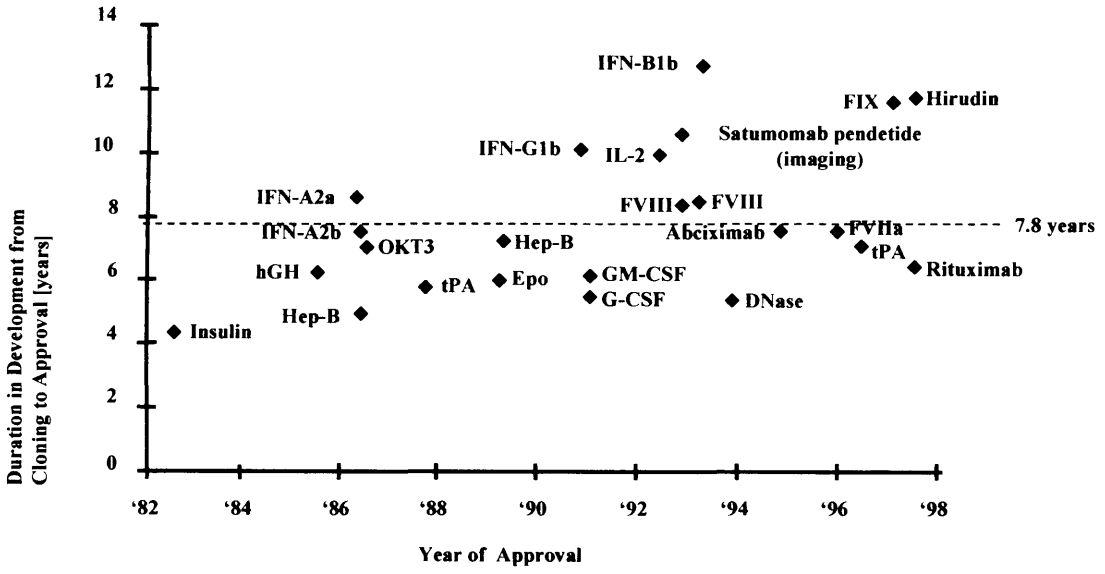
In a follow up study, Reichert (2000) provides the data for 26 biopharmaceuticals approved between 1995 and 1999 with a comparison of the mean phase lengths by product category, review status, orphan-drug designation and therapeutic indication.

Reichert (2000) concludes that the variation observed in the approval phase lengths is due to the review status (standard or priority) and not a result of therapeutic indication or product category. These are compared to the values of Gosse and Manocchia (1996). Reichert (2000) concludes that the mean approval phase for biopharmaceuticals has shortened from the 1980 – 1994 period to 1995 – 1999, while the mean clinical development phase has increased. The reason cited for the reduction of the approval phase is the same identified by DiMasi *et al.* (2003); the introduction of the Prescription Drug Use Fee Act of 1992 and the Food and Drug Administration Modernisation Act of 1997. The increase in the clinical phase is attributed to several reasons. They being the additional complexity of the disease interventions, the advancement of the technology used to manufacture and characterise the biopharmaceuticals and the high standards being established by the FDA.

The same reasons are suggested by Reichert and Paquette (2003) for the increase in the time length for clinical phase of recombinant proteins. Reichert and Paquette (2003) presented data on the time length of the clinical phases of recombinant proteins based on the year of clinical initiation and FDA approval. A total of 271 recombinant proteins in development and in the market were used for this study. Reichert (2003) analyses clinical development and approval data for 554 therapeutics (504 small molecules, 40 recombinant proteins and 10 MABs) approved from 1980 – 2001 in order to assess the effects of the regulation changes cited earlier. The author provides a breakdown of the therapeutic categories as well as the year of approval for the drugs investigated for easy comparison. The author states that the trends indicate that the effect of these regulation changes was to shorten the time to market from mid to late 1990s. However, the gains have not been sustained during the early 2000s.

While the approval phase has shortened the clinical development phase has increased and the reasons suggested are the same as Reichert (2000). Reichert and Healy (2001) compare the approval times of the EMEA in Europe and the FDA in the US of 27 biopharmaceuticals within the period of 1995 - 1999. The authors conclude that the approval time for all products was 13% faster in the EU compared to the US (10.6 vs. 12.2 months). This is despite the EMEA not having a prioritisation scheme for approval of therapies for life threatening diseases like the FDA.

Foo *et al.* (2001) using information available in the public domain published the time lengths of 25 biopharmaceuticals that had made it to the market (Figure 2.4). The time to market was defined as the estimated year of cloning till the date of approval. Foo *et al.* (2001) observed that there was no clear correlation between the time to market and the type or function of the drug. The authors identify the supply of material for pre-clinical and clinical trials as a critical issue that affects time to market and suggests that the planning for the production of material must occur before the efficacy of the product is established.



Dnase = dornase α	hGH – human growth hormone
EPO – epoetin α	IFN-α2a – interferon 2a
FVIIa – clotting factor VIIa	IFN-α2b – interferon α2b
FVIII – clotting factor VIII	IFN-β1b – interferon β1b
FIX – clotting factor IX	IFN-γ1b – interferon γ1b
G-CSF – filgratism	IL-2 – aldesleukin
GM-CSF - sargramostim	OKT3 – muromonab-CD3
Hep B – hepatitis B vaccine	tPA – tissue plasminogen activator

Figure 2.4 Time to market versus year of market approval for marketed biopharmaceuticals (adapted from Foo *et al.*, 2001). The figure indicates a wide variation of the development time and the average time for the 24 products is 7.8 years, which is close to the 7.5 years deduced by DiMasi *et al.* (2003).

Regulatory hurdles have been cited as a reason for increasing drug development time lengths (Foo *et al.*, 2001; Wechsler, 2002). However Zemmel and Booth (2004) state that while the regulations have got tougher, it has not affected the time lengths (Figure 2.5).

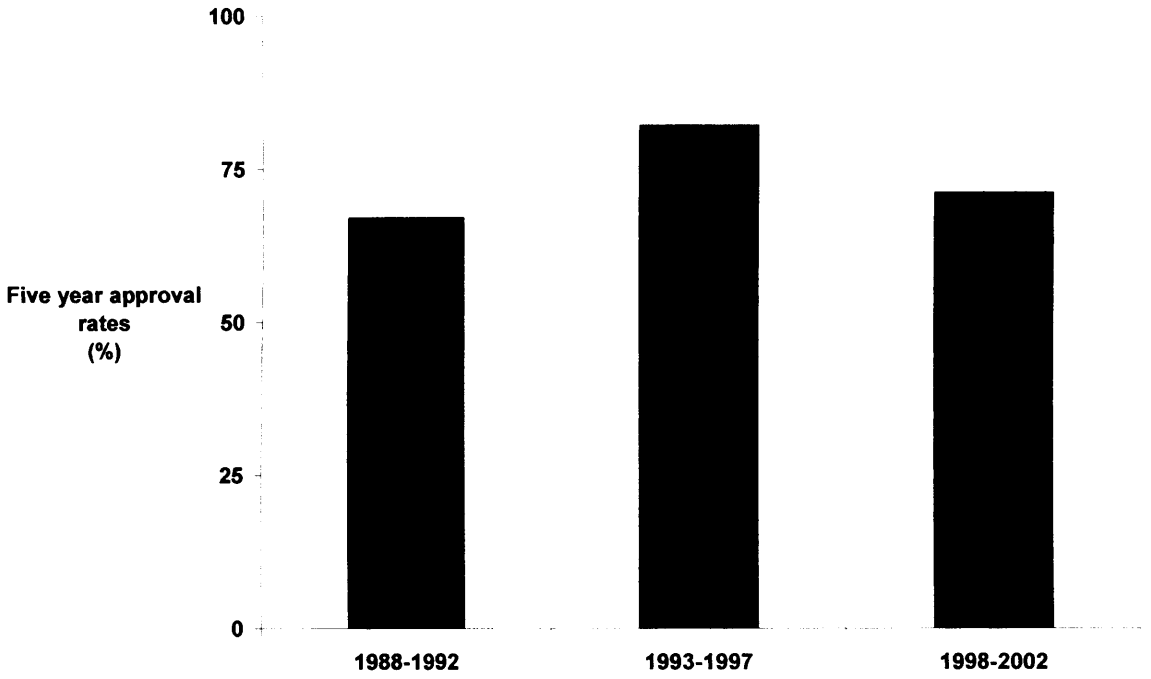


Figure 2.5 FDA's NDA approval rates during the past 15 years, where 70 – 80% of all of the NDAs submitted have been approved. The number of annual submissions and approvals were relatively constant and the data show that there has not been a significant increase in the approval time due to the FDA activities.

2.4.2 Cost of biopharmaceutical drug development

The importance of empirical analysis of the cost of drug development is highlighted by DiMasi *et al.* (1991). The authors raise four important reasons for doing so. First, knowledge of R&D costs is important for analysing issues such as the returns on R&D investment. Second, the cost of a new drug has direct bearing on the organisational structure of innovation in pharmaceuticals. Third, R&D costs also influence the pattern of international resource allocation. Finally, the cost of R&D has become an important issue in its own right in the recent policy deliberations involving regulatory requirements and the economic performance of the pharmaceutical industry.

The cost of producing new drugs, both chemical and biological, has been on the increase over the years (Stonebraker, 2002). The higher attrition rates during the development phase mean the drugs that do make it to the market have to pay for the drugs that fail. Research and development costs have grown 13% every year since 1970, a fifty-fold increase (Booth and Zemmel, 2004). During the same time period, the number of investigational new drug candidates and new drug applications has remained constant. In the 1950s, the norm for pharmaceutical companies was to invest ~5% of sales revenue in R&D; by 1980 this had risen to ~9%, and by 2002 the industry average was 16%, with some firms spending well over 20% (Booth and Zemmel, 2004).

Several studies have been conducted to estimate the total cost of taking a drug from discovery to market launch. DiMasi *et al.* (1991) presented one of the most comprehensive studies and was conducted mainly on new chemical entities (93 randomly selected drugs from 12 pharmaceutical companies). The authors estimated the pre-tax cost of an approved drug to be US$ 231 million (1987 dollars). Myers and Howe (1997) estimated the value of US$ 297 million (1994 dollars) for developing and launching a drug and this takes the cost of failed drugs into consideration, but the manufacturing and marketing costs are not included. The breakdown of these costs into different stages is presented in Table 2.8. While DiMasi *et al.* (1991) used data from companies, Myers and Howe (1997) used a financial model of the drug development process to estimate their values.

In a follow up study, DiMasi *et al.* (2003) calculated the cost to be US$ 802 million (2000 dollars) and took into account the cost of failed drugs in the portfolio. The pre-clinical cost was estimated at US$ 335 million and the clinical development cost at US$ 467 million. The breakdown of the costs to different stages is presented in Table 2.9. This is the most comprehensive study of this nature that is available in literature. Again it is based mostly on chemical entities. Stewart *et al.* (2001) provides a breakdown of the cost of clinical trials for biopharmaceuticals, with average cost per subject, but does not provide the cost of process development, manufacturing and marketing. The reason for increase in the development costs of pharmaceuticals have been attributed to the increase in clinical trials cost due to more test per patients and more patients per trial being used (Booth and Zemmel, 2004).

Table 2.8 Cost (1994 dollars) per approved drug by R&D phase in US$ millions (Myers and Howe, 1997)

	Discovery	Pre-clinical testing	Phase I	Phase II	Phase III	FDA Approval
Myers and Howe (1997)	16.71	64.28	11.63	20.20	28.34	4.39
DiMasi *et al.* (1991)	81.9		11.63	20.20	28.31	

Table 2.9 Average clinical period capitalised cost (2000 US dollars) for investigational compounds (DiMasi *et al.*, 2003)

Phase	Capitalised expected phase cost (US$ million)
I	30.5
II	29.5
III	37.4
Long-term animal	3.0

2.4.3 Risk in drug development

The pressure on R&D is such that on the one hand, the pipeline is required to produce a large number of innovative products in a short time; on the other hand, new products need to be more innovative than in the past (Chiesa, 1996). Due to the highly regulated nature of the industry the probability of failure is high and this attrition has been cited as reason for the loss in productivity in the pharmaceutical industry (Booth and Zemmel, 2004). Grabowski and Vernon (1994) investigated the development of new pharmaceuticals (chemical entities) and concluded that seven out of ten marketed products do not recoup their original investment.

Drug candidates could fail at any point of the development process or even after it has been launched in the market. The latter would be a failure in a commercial sense, where the investment made on the drug is not being recovered. Sager (2001) points out that the marketplace itself is comprised of multiple tiers of demand channels: from pharmaceutical manufacturers to drug wholesalers, from pharmacy retailers to physicians, from patients and patient advocacy groups to managed care organisations. The introduction of new therapeutic product often depends upon a carefully balanced sales and marketing campaign leveraged through all these potential channels. The failure during clinical development could be due to the fact that the drug is not presenting enough evidence to support the efficacy levels or the toxicity being too high. The inability to develop a manufacturing process that would enable the drug to be manufactured economically is another reason for failure. The collapse of a drug development program at a late stage will incur losses running into millions of dollars. Given that development costs are very high and continuously grow, killing projects at early stages is increasingly critical (Chiesa, 1996).

Many attempts have been made to assess the risk that is present in the drug development process (Struck, 1994; Gosse *et al.*, 1996; Reichert, 2001; DiMasi *et al.*, 2003). One method of quantifying the risk is to compute the phase transition probability, which refers to the likelihood that an investigational drug will progress in testing from one phase to the next. The overall clinical approval success rate is the probability that a compound that enters the clinical development will eventually make it to the market. Struck (1994) presented phase transition probabilities for biopharmaceuticals and were based on information gathered from the public domain. Nicholson (1994) published the probability of reaching a market from different phases and these were based on discussions made with industrial personnel. Gosse *et* al. (1996) presented the phase transition probabilities for recombinant proteins and therapeutic monoclonal antibodies in clinical trials between 1980 and 1994. The data gathered for this study was sourced from the European Medicines Evaluations Agency (EMEA) and the US biopharmaceuticals database, both of which are maintained by the Tufts Center for the Study of Drug Development (Tufts CSDD). The authors concluded that recombinant proteins and new chemical entities had similar failure rates for the time period 1980 – 1989. DiMasi *et al.* (2003) calculated the phase transition probabilities for new drugs in different stages of development

(Table 2.10). As these data are based on new chemical entities they do not truly represent the nature of biopharmaceuticals. However DiMasi *et al.* (2003) remains the most comprehensive study that has been undertaken. Booth and Zemmel (2004) suggest that biologics have had 70% higher clinical survival rates than small molecules.

Table 2.10 Phase transition probabilities for new drugs in development (DiMasi *et al.*, 2003)

Phase	Probability of entering Phase (%)
Phase I	100.0
Phase II	71.0
Phase III	31.4
Long-term Animal Studies	31.4

There are two other publications of research that were conducted on the failure rates of biopharmaceuticals. Reichert (2001) published the phase transition probabilities for monoclonal antibodies (MABs) using data collected on 182 MABs which were in the market and at different stages of clinical development (Table 2.11). The source for this data was again the databases maintained by Tufts CSDD.

Table 2.11 Phase transition probabilities for monoclonal antibodies (Reichert, 2001)

Monoclonal antibody type	Phase I to II (%)	Phase II to III (%)	Phase III to Review (%)	Review to Approval (%)
Murine Mabs	77	52	45	33
Chimeric Mabs	86	40	80	100
Humanized Mabs	84	72	75	100
Average	82.3	54.7	66.7	77.7

In a later and more detailed study Reichert and Pavlou, (2004) published the overall success rate of monoclonal antibodies (Table 2.12) but did not revise the phase transition probabilities for MABs. Reichert and Paquette (2003) presented the overall and phase transition probabilities for recombinant proteins (Table 2.13). The probabilities regarding recombinant proteins were based on 271 rDNA therapeutics that entered clinical study during 1980 – 2002 and are divided into the different

therapeutic categories. This is the most comprehensive study done on biopharmaceuticals that is available in literature currently. In all of the studies mentioned above, the authors conclude that in time with more data being available the probabilities will change and be more valid.

Table 2.12 Overall success rates for MABs (Reichert and Pavlou, 2004)

MAB type	Overall success rate (%)
Murine Mabs	4.5
Chimeric Mabs	26
Humanized Mabs	18
Human	14

Table 2.13 Probabilities for clinical and U.S. review phase transitions for therapeutic recombinant proteins (Reichert and Paquette, 2003)

Recombinant protein	PI to PII (%)	PII to PIII (%)	PIII to US review (%)	US review to approval (%)
Anti-infective (n = 27)	69	53	86	83
Antineoplastic (n = 36)	90	41	57	100
Wound/burn healing (n = 14)	86	70	75	100
CV/Haemostasis (n = 45)	90	69	71	100
Blood cell deficiency (n = 23)	83	79	50	100
Immunological (n = 34)	93	67	78	100
Enzyme replacement (n = 16)	93	56	100	100
Endocrine (n = 52)	87	94	79	100
All products (n = 271)	89	69	65	97

2.4.4 Rewards in biopharmaceutical drug development

The rewards when a drug candidate succeeds in getting into the market are significant. A blockbuster drug on average would return over a US $1 billion per year during its peak sales. In turn this money could be invested back in the other drugs in the portfolio. Blockbusters alone contributed almost 50% of the total revenues of Pfizer, AstraZeneca, Eli Lilly and Schering-Plough in the year 2000 (McNamara, 2002). This provides an understanding of the high rewards that await a successful drug in the market.

Protein-based therapeutics generated more than US$13.3 billion of sales in 2000, which was an increase of 23% from US$10.9 billion in 1999 (Ginsberg *et al.*, 2002). The revenue from biological products worldwide had increased to US$ 41 billion in the year 2002 (Ernst & Young, 2003). Table 2.15 lists the sales generated by 24 major protein therapeutics in the year 2003. The FDA in 2002 approved 9 biologics within the US, and in 2003 a total of 14 biologics received approval for market launch. Table 2.14 lists a set of drugs and that are expected to be generating high revenue in the future (Burrill and Company, 2004b).

Table 2.14 Biopharmaceuticals that are expected to generate high revenue in the future (Burrill and Company, 2004b)

Drug	Company	Indication	Peak potential ($M)
Genaissance	Genta/Aventis	Melanoma	200 – 500
Cinacalet	Amgen/NPS	Hyperparathyroidism	300 – 500
Anidulafungin	Vicuron	Fungal infections	200 – 300
Symlin	Amylin	Type II diabetes	200 – 300
Exenatide	Amylin/Eli Lilly	Type II diabetes	500 –1000
Gilead	Viread/Emtriva	HIV	500 – 1000

Table 2.15 Highest revenue generating therapeutics of 2003 (Burrill and Company, 2004b)

Drug	2003 Sales (US$M)	Company	Disease
Epogen	2435	Amgen	Anaemia
Rituxan	1982	Genentech and Biogen-IDEC	Non-Hodgkin lymphoma
Aranesp	1544	Amgen	Anaemia
Enbrel	1300	Amgen and Wyth	Arthritis
Neupogen	1267	Amgen	Neutropenia
Neulasta	1256	Amgen	Neutropenia
Avonex	1168	Biogen	Multiple sclerosis
Synagis	849	Medimmune	Infectious disease
Rebif	819	Serono	Multiple sclerosis
Cerezyme	739	Genzyme	Gaucher disease
Viread	567	Gilead	HIV
Gonal-f	526	Serono	Infertility
Herceptin	425	Genentech	Breast cancer
Growth hormone	322	Genentech	Growth hormone deficiency
Provigil	290	Cephalon	Excessive daytime sleepiness
Renagel	282	Genzyme	End stage renal disease
Actiq	237	Cephalon	Breakthrough cancer pain
Fluvirin	219	Chiron	Influenza
AmBisome	198	Gilead	Infectious disease
Betaseron	189	Chiron	Multiple sclerosis
Integrilin	184	Millennium	Acute coronary syndrome
TOBI	172	Chiron	Cystic fibrosis
Saizen	152	Serono	Growth hormone deficiency

2.5 THE FUTURE OF BIOPHARMACEUTICAL DRUG DEVELOPMENT

2.5.1 Biogenerics

The biopharmaceutical market has come along way since 1982 when the first biopharmaceutical product, recombinant human insulin, was launched. As patent protection expires for the first wave of biopharmaceutical products, the potential marketplace for generic substitutes looms large. Biogenerics offer a multi-billion dollar marketplace which has yet to be exploited (Polastro, 2004). Biogenerics are essentially similar to the original product and involve an active substance with an expired patent. There is little or no sales promotion involved with biogenerics and they could be approved through a simplified abbreviated registration process. To be first on the generics market, patent windows need to be identified and utilised during the development strategy in order to avoid infringement battles (Maleck and Pollano, 2001). A good example of this is the Merck-Amgen EPO dispute in the 90s, which eventually allowed Merck to develop EPO because of a smart patent avoidance strategy. At least 8 of the highest selling biopharmaceuticals have generic versions being developed currently (Burrill and Company, 2004b). Assuming a similar penetration to that of the traditional drugs, the market for biogenerics has been estimated at US$ 2 billion (Maleck and Pollano, 2001).

However there are many barriers that have to be overcome if the biogenerics market is to realise its said potential. The main barrier is from the regulatory authorities. As the manufacturing process and the expression cell system are unique to each product, the authorities would require clinical trials to be performed for the biogenerics. Still the cost would be lower due to fewer failure rates and less research during development. Of the US$ 803 million it costs to develop the average drug, only about five to 10 per cent of those costs will be incurred by a re-developer (BCG Focus, 2001). Other challenges that biogenerics has to overcome include the requirement of a high level of specialised skills and competencies; the willingness to dedicate long-term financing; and extensive planning - something not commonly found in the somewhat short-sighted generics industry (Maleck and Pollano, 2001). Given the value of the biopharmaceuticals, the original companies would use multiple patents of the product as well as the process to protect their portfolio.

2.5.2 New opportunities

Sequencing the human genome has been described as the single most important event in the history of human health care and has provided enormous opportunities. Leveraging the 40,000 – 72,000 genes that have the greatest potential will serve as the foundation for developing personalised medicines and fundamentally change the way new biopharmaceuticals are identified and developed. Pharmacogenomics is the science of developing a customised and personalised medicine (Sager, 2001). According to some estimates the human genome has around 3,000 drugable targets (Booth and Zemmel, 2004). The vast amount of knowledge about genes, proteins and the biology of disease that has been created by the sequencing of the genes are thought to be so much that the ability to meaningfully use this data is not possible at the moment (Sager, 2001). Therefore it has been suggested that information regarding genes, proteins mRNA, ADMET and clinical trials must be linked across platforms and broadly utilised (Genetic Engineering News, Dec 2001). It can be said that the strategic issue facing drug discovery is not the availability of genome data, it is the ability to transform the data into information with biological and therapeutic significance. Booth and Zemmel (2004) agree stating that if these genomic targets are not properly scrutinised early, companies could end up with high failure rates down the development pathway and increased losses.

Using a combination of embryonic stem-cell technology and retroviral therapy, it may soon be possible to design new functions in aging or diseased organs, to grow new cells, tissues and organs from scratch (Sager, 2001). Further in the future, there could be alternatives to conventional protein production; for instance, pharmacologists will use the protein as a template for rational, small chemical drug design (Greener, 2001).

The age factor is playing an important role, with a higher percentage of the population being in the 60 – 90 age group it is estimated that there are over 200 drugs (both chemical and biological) being developed for age related diseases. Other areas of the market where more companies are concentrating their research are obesity, Alzheimer's, antibiotic resistance and wellness. The last category of wellness refers to preventative cure. Another area that is being pursued is 'feel-good' drugs, for example, male pattern baldness and wrinkle removing.

2.5.3 Transgenic expression systems

One of the challenges created by the biotechnology revolution is the development methods for the economical production of highly purified proteins at large scale. Transgenic animals could emerge as an important source of therapeutic proteins, probably in another decade (Greener, 2001). These transgenic animals are expected to acquire a large slice of the protein market. The ethical issues concerning the use of transgenic animals are supposed to be overcome due to the fact that they are being used for therapeutic uses and not as a source of food. Watler (2001) provides a comprehensive comparison of the cost and capacity of transgenic and cell culture production systems. The author states that 25 – 30% savings could be made on the cost of goods (COG) using transgenic systems as opposed to a bioreactor. However in this study the additional facility, regulatory and development costs were not accounted for. When the capacities are taken into consideration, it is claimed that the transgenic systems are capable of producing high quantities (multi-tonne capacities), but the feasibility of field/farm GMP operations have not been fully demonstrated.

Dove (2002) provides a comparison of the raw materials cost of different expression systems with the benefits of the use of transgenic animals being highlighted. Again, the costs are very low compared to the mammalian cells ($2 compared to $150). Hood *et al.* (2002) presents another comparison which agrees with the above values. Pollock *et al.* (1999) provides a description of the use of transgenic milk as method of production of recombinant antibodies and argues that it is possible to achieve high-level expression of active recombinant immunoglobulins and immunoglobulin-fusions in the milk of transgenic animals. The author points out the scale-up flexibility and low costs (increasing or decreasing the herd) compared to more traditional cell culture facilities. The feasibility of using different animal species (mouse, rabbit, goat etc...) for the production of milk is presented with the comparison of reproductive age, average yield etc...

Protein production in plants is a means of resolving the dilemma of mammalian cell manufacturing capacity. The number and types of antibodies expressed in plants has increased steadily since the first reports of this accomplishment in the 1980s, illustrating the versatility of plants as a production system for antibodies (Hood *et al.*, 2002). The authors compare the process of manufacturing in different systems (CHO

cells and transgenic animals) to manufacturing in plants and conclude that the advantages of using transgenic plants are capital cost savings, ability to scale up or down depending upon the market demand, freedom from human pathogens and savings on cost of goods. The next section provides a brief overview of the organisational changes that are made in order to minimise the risk and maximise rewards by companies involved in drug development and manufacturing.

2.5.4 Strategic partnering

Many organisational changes are being made in the industry in order to increase the productivity of the companies and minimise the effects of risk in drug development. By partnering with a company that knows the market, understands the regulatory requirements a start-up biotechnology company can reduce its risks and minimise adding heavy overheads (Humphrey, 1996). Worldwide there were 600 publicly traded biotech companies in 2002, which made a combined loss of more than US$ 12 billion (Ernst and Young, 2004). Becoming a fully functional pharmaceutical company for example in the mould of Amgen and Genentech, for a small start-up company is still a possibility, but risky and expensive (Ernst and Young, 2004). Given this uncertain environment, many companies, both large and small, seek to form strategic alliances.

The strategic decisions available take many forms. In licensing refers to adding a new drug candidate from outside to a company's product portfolio. This could be done to increase the therapeutic areas a company has in its portfolio as well as a back up for drugs that can fail. Other deals could involve strategic partnering, where the development of products are shared in order to make available better resources for research and development as well as manufacturing for a product. In the year 2003, five such deals were arranged for Phase I products, each valued at over US$ 100 million (Burrill and Company, 2004b). Mergers refer to companies merging to form a larger company in order to expand the product portfolio as well as the resource base. Acquisitions are made by larger companies in order to expand their product portfolio. In the US all such deals are regulated by the federal trade commission (FTC). Table 2.16 provides a list of the mergers and acquisitions that took place in the year 2003.

Table 2.16 The main mergers and acquisition deals that took place during 2003 (Burrill and Company, 2004b)

Companies involved	Value of the deal (US$ million)
Johnson and Johnson/Scios	2400
Roche/Igen	1400
Pfizer/Esperion	1300
Roche/Disetronic	1200
Chiron/Powderject	879
Novartis/Idenix	612

2.6 CONCLUSIONS

This chapter has described the process of biopharmaceutical drug development, which is a lengthy and costly one. The different activities that are involved in taking a drug from discovery into the market have been discussed. The cost of drug development has seen an increase over the years, culminating in pharmaceutical companies increasing the amount of money spent in research and development. The number of biopharmaceuticals in the market has been increasing steadily and these generate high revenues to the developers.

The state of manufacturing currently in the industry has been reviewed. There is much capacity being built around the world with products in the pipeline to utilise the new capacities. The risk and the uncertainty present in the process of drug development have been explored. Quantifying the risks helps decision-making. Attempts to quantify these risks have been discussed in Chapter 1. The next chapter describes the conceptual framework and the implementation of a prototype tool to model the drug development process in order to aid decision-making in managing the drug development and new drug candidate selection.

CHAPTER 3

DESIGN AND IMPLEMENTATION OF THE TOOL

3.1 INTRODUCTION

As indicated in the preceding chapters, the high uncertainty in drug development has initiated many attempts to contain costs, reduce the time to market and reduce the losses due to failure of drugs at different stages in the development process. In this chapter a conceptual framework to model the process of biopharmaceutical drug development and manage the product portfolio is presented. This is then followed by a description of the implementation of the framework into a decision-making software tool.

This chapter is divided into eleven main sections. Section 3.2 provides a description of the biopharmaceutical drug development domain that is addressed by the framework/tool. The scope of the framework is indicated in Section 3.3. In Section 3.4, the modelling approach taken is described. In the next two sections the key features and parameters are summarised. In Section 3.7 the different software platforms are assessed briefly for the implementation of the framework. A tool overview in Section 3.8 is followed by a detailed description of the components in Section 3.9. The approach to modelling uncertainties in the tool is described in Section 3.10. Finally a summary is provided in Section 3.11.

3.2 DOMAIN DESCRIPTION

The key features of drug development and portfolio management are identified in this section. As the cost of research and development of new drugs is on the rise, simulation tools can be used to capture the tasks, resources, business issues and uncertainties involved in drug development and thus compare different portfolio management strategies.

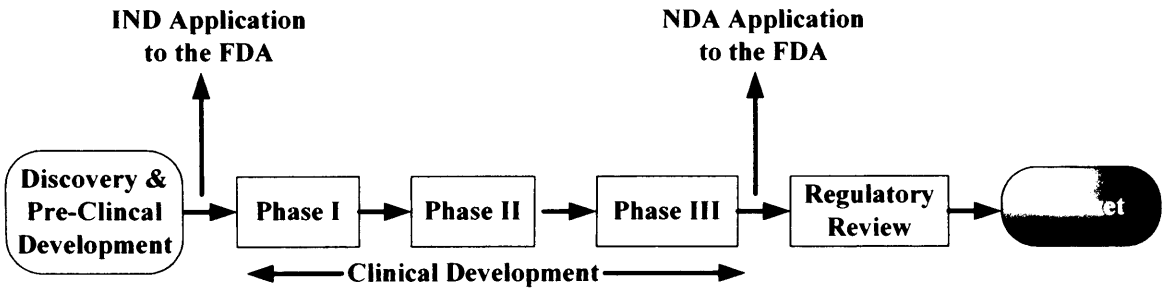


Figure 3.1 The process of drug development, which is comprised of a set of sequential well-defined phases that increase in complexity.

Figure 3.1 presents the main phases involved in taking a drug into the market. For each of these phases there are a range of activities that are carried out requiring extensive levels of resources. In the pre-clinical phase a large number of molecules are extensively screened for potential drug candidates. Once a molecule has been identified as having both the potential to cure a disease as well as generate revenue, it is taken into clinical development where it is subjected to a series of tests to ensure it is both safe and effective in achieving its claimed therapeutic effect(s).

During Phase I, initial process development is carried out to produce the material in small (gram) quantities. The process and product development work at this phase also concentrate on the establishment of new analytical methods. Given the high uncertainty at this initial stage, minimum process development is carried to get a reproducible process in order to reduce losses in case of early product failure. However, any significant deviations from the initial protocol to generate material at a later stage could invalidate earlier results. Manufacture at Phase I is usually carried out at lab-scale or pilot-scale. Clinical trials are conducted in 20 – 80 healthy volunteers to identify toxic effects, if any. This Phase on average would take 1 – 2 years.

Drug candidates that are deemed safe would then proceed to Phase II, where further process and product development is carried out, building on the work done earlier. The manufacture of material for these clinical trials and other development work is carried out at pilot plant scale. The clinical trials are tailored to confirm the stated

efficacy of the drug. This involves approximately 100 – 300 patient volunteers. Phase II would take 1.5 – 2 years on average.

Phase III is the longest and costliest phase. Process development work is concentrated on ramping up the production from pilot-plant scale to large scale. The clinical trials will involve 1000 – 3000 patient volunteers. Therefore the manufacturing has to be carried out at large scale. The aim of these clinical trials is to confirm effectiveness in a larger sample and to identify minor adverse reactions from long-term use. Phase III would take on average 2 – 3 years for completion. The equipment, facility and the assays all need to be fully validated at this stage.

Failure of the drug candidate could occur at any stage of the development process. The inability to develop an economically feasible process, low yields and titres are reasons for failure related to process development. Batch failure due to contamination could result in manufacturing delays. The drug's low efficacy level and any adverse side effects could cause the drug to be abandoned after clinical trials.

If the results from the Phase III clinical trials are deemed successful, a new drug application (NDA) is filed with the FDA for final approval. Once the FDA approval is granted, the drug is then marketed. At each step, resources have to be allocated for successful completion of the phase and decisions have to be made as to whether the drug candidate is carried forward, held back for a time period or dropped from the portfolio. The resource level of the company and its strategy will also decide the number and the type of drugs being held within its portfolio.

For process development, a cross functional team would have to be employed. The manufacturing strategy for each phase of the development cycle has to be set in order to have material ready initially for pre-clinical/clinical trials and then for the market. This would involve making decisions about where to invest, in production facilities or to find appropriate contract manufacturers. Since changes to the FDA regulations in 1996, biological products can be produced at any facility and is not confined to a single licensed facility. Therefore purpose-built facilities do not have to be built prior to product approval and early commercial production can take place in a contract

facility. Clinical trials have to be planned ahead with clear objectives. They form the costliest aspect of drug development. Given the high level of risk and uncertainty, planning the development work and the resource allocation have to be carried out to minimise the effect of any failure of drugs. A computer-aided tool capable of capturing the risk and the rewards of different strategies can help provide a rational basis for confident decision-making in biopharmaceutical drug development planning and portfolio management.

3.3 SCOPE OF FRAMEWORK

Defining the scope of the modelling effort was a key initial step required to focus simulation efforts and to ensure the breadth of the analysis was not too wide that it became too complex to handle. As stated earlier, the purpose of the simulation tool is to assess the impact of different strategies on a portfolio of biopharmaceutical drugs proceeding through development. More specifically, the scope of the modelling framework was defined as follows:

- To simulate the development of new biopharmaceuticals

The tool should be able to model the process of a drug being taken through all the development phases and, if successful, its performance in the market. This should enable the user to calculate the cost and the time to market of developing a particular drug.

- To prototype different management strategies before implementing in real life.

Given the number of critical decisions that has to be made during the development stages of a drug, the tool has to be able to be used to test each of these new decisions prior to implementation. For example, given the limited levels of resources, both human and capital, available for drug development, different allocation patterns could be tried out in order to decide the best strategy for allocating resources.

- To conduct risk and profitability analysis

The risk in drug development can be quantified so as to compare different strategies. For example, comparing the value and risk associated with different drug portfolios.

In summary, the tool will provide the basis for a better decision-making strategy. What follows in the next section is a description of the approach adopted to model the process of biopharmaceutical drug development.

3.4 MODELLING APPROACH

A structured model of the biopharmaceutical development pathway was used in order to facilitate rapid modelling of the impact that business and process decisions made during the management of biopharmaceutical product development have on the portfolio profitability and risk. Figure 3.2 provides a simplified schematic of the proposed model.

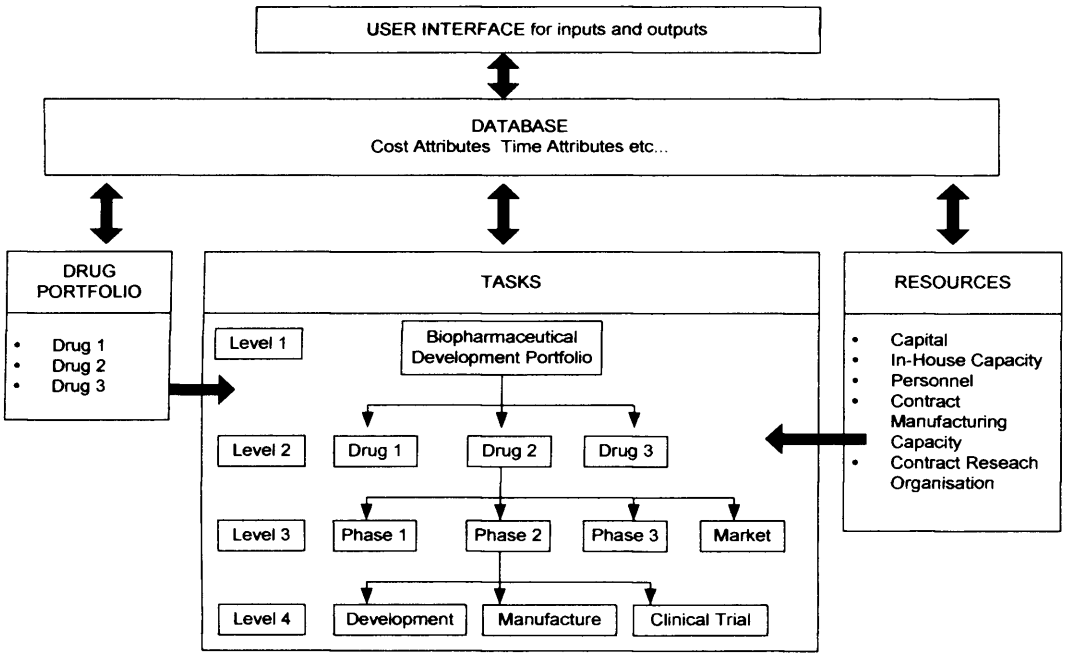


Figure 3.2 Simplified schematic of the main components of the proposed framework.

The framework seeks to integrate various aspects, including resource management and the development and manufacturing activities required for clinical trials as each relate to strategic decision-making. The model structure was arranged in a hierarchical manner to represent the key tasks of the biopharmaceutical drug development process through a series of levels increasing in complexity (Figure 3.3). The hierarchical structure enables the user to prototype a management strategy at the required level of detail, for example high level for executive decision-making and lower level for process decision-making. In addition it enables to simulate a series of 'what –if scenarios' rapidly. It also allows the user to access a breakdown of the model outputs. Therefore the costs and durations of specific tasks (e.g. cost and duration of clinical trials of Phase I) are available for analysis or comparison.

The hierarchical task representation also provided the flexibility to extend the task tree further without compromising tool functionality. With more information, each level activity could be broken down into sub-tasks that generated more accurate values for key parameters. This type of modelling framework is attractive in that it reflects the organisational structure of a drug company with longer term strategic planning at a corporate level and campaign planning at a development level. This makes for more efficient models requiring less maintenance and of greater accuracy. A similar approach has recently been employed to model the manufacture of biopharmaceuticals (Farid *et al.*, 2000; Farid, 2001; Farid *et al.*, 2001; Lim *et al.*, 2004; Mustafa *et al.*, 2004). A hierarchical solution approach was also proposed by Levis and Papageorgiou (2004) for multi-site capacity planning under uncertainty in the pharmaceutical industry.

The framework comprises the tasks involved in taking a drug to the market (e.g. development work, manufacture, clinical trials) and the resources required to carry out each task (e.g. capital, in-house capacity, personnel, contract manufacturing capacity). At the top-most level of the tasks the portfolio of drugs is modelled, which then breaks down into the projects handling individual drug candidates. At a greater level of detail the three phases of development and the market features are modelled for each drug. As depicted in Figure 3.2, the model includes the development process, manufacture and clinical trials associated with each phase. At the next level, the activities that make up the above different tasks are modelled. Each activity will have different inputs of time and cost. For example, the development phase would consist of the number of people working on a drug candidate, the yields achieved and the time spent in process development. Under the manufacturing tasks, production facilities and contract manufacturers are modelled. For each of these activities a series of decision points were defined and relevant attributes assigned.

The framework captures the interaction between the drug development tasks and the resources required for each drug in the portfolio. The resources are connected to all the tasks in the model, which in turn enables the activities to draw on the resources on the basis of availability. Resources are entities that are consumed or used by activities either in order for the activity to be completed or as a consequence of the activity being completed.

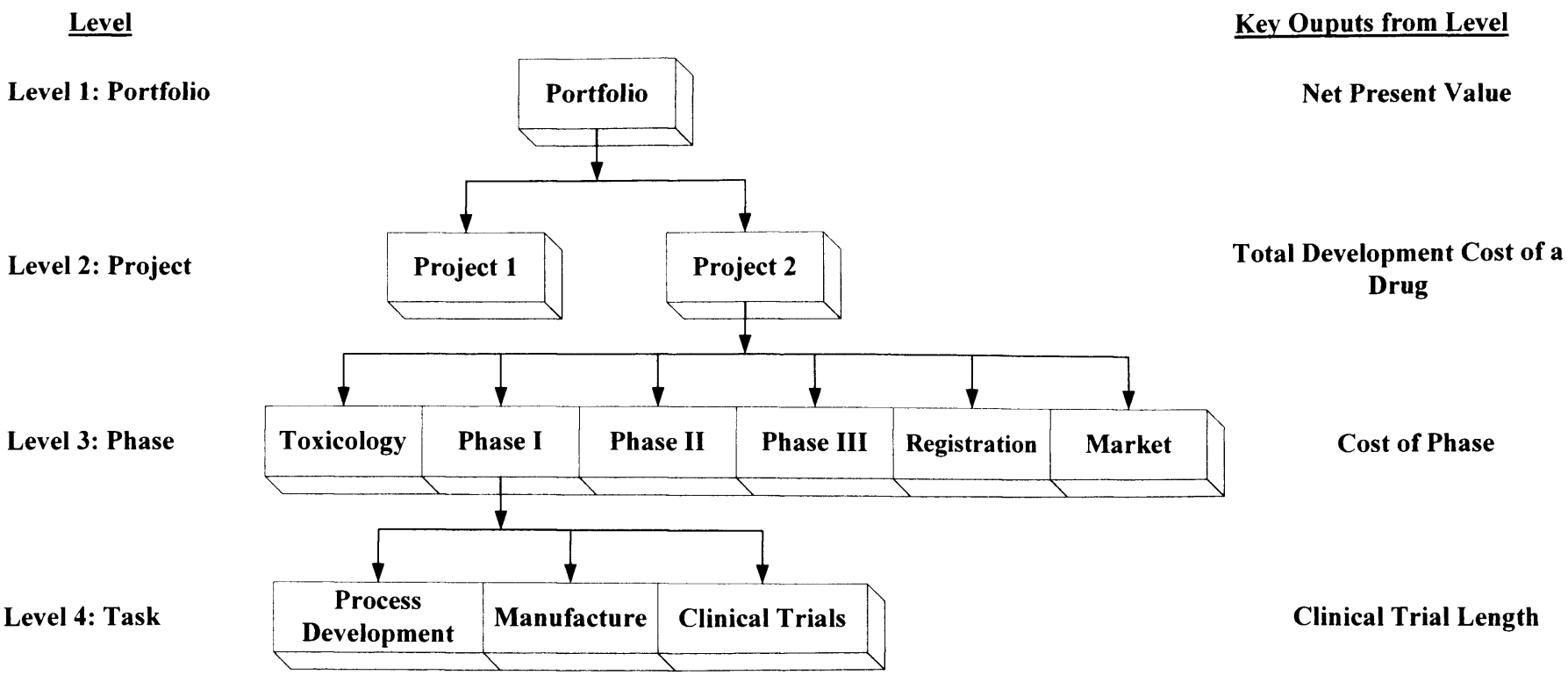


Figure 3.3 Hierarchical representation of the biopharmaceutical drug development pathway. This approach allows new levels of detail to be added as required by the simulation.

In addition, the attributes are stored in a database that the user can access. Default values for task durations and costs, as well as probability of failure are provided as part of the knowledge repository. The outputs of the model are exported into the database and saved during the simulation.

The model is flexible in order for simulations of alternative strategies to be investigated at all levels of decision-making. This involves the ability to model decision-making, evaluating alternatives for both stochastic and deterministic processes at different levels of detail. A robust modelling framework will reconcile the different metrics computed at different levels of the modelling hierarchy.

All the outputs from each level would add up through the hierarchical level through the use of common parameters running through all the levels, namely cost and time. However, useful outputs will be generated, summarised and presented from the lower levels as well, for example the human resource utilisation profiles for process development staff for Phase I. A summary of the typical outputs from each level is shown in Table 3.1.

3.5 KEY FEATURES

To satisfy both process development and business applications, each level defined the drug development process in terms of the tasks, the resources available and the drug candidates that proceed on the development pathway. Outside these core knowledge requirements existed characteristics that are more specific to each individual application. For process applications, examples include manufacturing data. Business applications require cost data and knowledge of resource utilisation and availability. The developed framework allows the user to investigate different production strategies in terms of the cost of development, time to market, resource use and profitability indicators such as net present value of the portfolio of projects. A systematic approach was used to map out the interaction between the different drug development activities.

Table 3.1 Summary of typical outputs from each level of the proposed framework

Level	Outputs
Portfolio	Number of drugs
	Portfolio cost
	Net present value (NPV)
Project	Total development cost of a drug
	Time to market for a drug
	NPV of a drug
Phase	Duration of each Phase
	Cost of each Phase
Task	Cost of process development, manufacturing and clinical trials
	Duration of process development, manufacturing and clinical trials
	Resources utilisation profiles

3.5.1 Tasks

Each block in Figure 3.2 represents an activity or task performing operations that generally consume resources and may also produce resources for use by later tasks. A task could be broken down into subtasks as required. Therefore a task block could represent a collection of activities at a high-level or a single activity at lower level as indicated in Figure 3.3. The information available and the desired outputs of the analysis determined the level of detail adopted to represent a task. As a minimum, each task was characterised by its duration.

The framework was designed to run tasks both concurrently and sequentially in multiple plans to allow the modelling of portfolios, since the development pathway for many drugs can be considered. Precedence relationships for the tasks were set, which meant that one task could not begin until another was completed. For example, the clinical trials could not be started till the required quantities were manufactured. The possibility of tasks overlapping was allowed where possible. The functionality to

represent alternative sequences of tasks, which maybe executed based on decisions, for example alternative manufacturing routes, was made available.

3.5.2 Resources

The drug development process requires a wide variety of resources. These include both renewable (e.g. personnel and facilities) and non-renewable (e.g. capital) resources. During a simulation the model calculates the need for and then request resources. The availability of resources acted as a constraint for the different tasks. The ability to outsource some of the developmental activities was incorporated. For example if the internal manufacturing facilities (resources) were not available, the ability to contract out was included. The ability to model flexibly resources along with their respective usage pattern is a key requirement in most simulation applications. The framework had the capability to monitor the availability, usage and replenishment of resources that are consumed by tasks.

During a simulation, the tasks in the drug development process request resources. The production or consumption of material or the status of a resource could define the availability of these resources. Resources therefore act as constraints on the process. If the resource was unavailable, the task could be delayed. An example of a resource category whose status restricted its use is personnel; the personnel could be busy with the development work of one drug and therefore the drug candidates following would have to be held back until the personnel needed became available. Another feature that was incorporated was the temporary availability of resources. For example, the shift patterns of personnel could be defined, where staff would be available only for a given period of time each day.

3.6 KEY PARAMETERS

All the features described in the modelling approach had input and output parameters, or attributes. The following measures were considered critical for assessing the capabilities and limitations of alternative drug development strategies: cost, time to market, risk and net present value of the portfolio. These are closely interrelated.

3.6.1 Cost

Costs include the capital expenditures and investments that would accumulate when a company undertakes the development of a new drug candidate. Capital costs would include the cost of building facilities for carrying out research and development, manufacturing for clinical trials and the market itself. Manufacturing costs for material manufactured for clinical trials were accounted on a cost per batch basis (personnel communication, Rebecca Paulraj, Lonza Biologics, Slough, UK, Peter Ketelaar, DSM Biologics). This included all the material costs as well as operating costs. In costing for the manufacture of material for the market, the cost of goods per gram was used, as is the case in the industry (Farid *et al.*, 2001; Lim *et al.*, 2004). Other costs include process development and clinical trials and marketing. These were collected through literature (DiMasi *et al.*, 2003; Stewart *et al.*, 2001) and through conversations with industrial experts (personal communication, Rebecca Paulraj; Steve Froud, Lonza Biologics, Slough, UK; Peter Ketelaar, DSM Biologics).

3.6.2 Time

The duration of each task was either given as an input or was computed based on the inputs or distributions entered. These durations were summed to calculate the time to market for the product. This enabled the different parameters that affect the time to market to be investigated further. The duration of a task was affected by resource constraints that could delay tasks until resources became available. Monitoring activities over time also permitted the generation of resource utilisation profiles. These could be used to assess whether modifications to operations would help to reduce bottlenecks in the drug development process. The global time unit of the framework was set to weeks, which allowed tasks to be modelled at a detailed level. At the top most strategic level the outputs were in years.

3.6.3 Profitability indicator

To quantify the success of drug development and compare different strategies an output of the simulation process is required. The net present value (NPV) was used as the main indicator of profitability in the process of drug development. The NPV refers to the present value of an investment's future net cash flows less the initial investment (Peters and Timmerhaus, 1991). The NPV calculated by the model is useful in comparing different management strategies or drug candidates in a

portfolio. The steps involved in the NPV calculation and the assumptions are presented in Chapter 4.

3.7 ASSESSING SOFTWARE PLATFORMS FOR IMPLEMENTATION

Once the conceptual framework was developed, the next stage involved selecting a suitable software platform to translate the framework into a computer-aided tool. As the key process and business features (e.g. tasks, costs and uncertainties) of the drug development process were identified, the requirements for the software platform to be used were specified. Past work at the Advanced Centre for Biochemical Engineering, University College London (UCL), had focused on using ReThink, a graphical application that runs in G2 (Gensym Corporation, Cambridge, Massachusetts, USA), an object-oriented programming environment (Farid, 2001; Karri *et al.*, 2001). Key advantages of ReThink were the useful pre-built features that enable extension and customisation for process re-engineering. Such a package facilitates rapid prototyping for process development in a modular and hierarchical fashion by describing the manufacturing activities at various levels of abstraction. However, one of the key disadvantages was found to be that the package is extremely programming-intensive.

The suitability of many software platforms for a similar type of simulation work was investigated extensively by Farid (2001). The required capabilities of the modelling language were divided into two categories, "declarative and procedural knowledge", representation capabilities and "dynamic behaviour" capabilities (Farid, 2001). The declarative and the procedural knowledge refer to the properties and functions of a task in the drug development process. For example, the process and product development task's properties include its cost, duration and an output of the yield achieved. The dynamic behaviour capabilities relate to time-dependent operations that the language must be able to perform so as to visualise the process logistics and analyse its performance. An example of information that must be updated in "real time" is resource availability, since this affects the allocation of resources to tasks over time. This is important for tasks competing for specific resources since the tasks can become delayed by the non-availability of a resource. Table 3.2 summarises the requirements for the software language.

Table 3.2 Requirement specifications for the tool (adapted from Farid, 2001)

Requirement type	**Specification**
Representation of declarative and procedural knowledge	Tasks and their characteristics
	Resources and their characteristics – resources include capital, facilities and personnel
	Drug candidate flow and its characteristics
	Relationships between tasks, resources and material flow
	Sequences of tasks
	Resource requirements for each task
	Calculation procedures for material production
	Variables for the calculation procedures
	Time
	Hierarchical views of the tasks
	Risk/uncertainty: stochastic variables defined using probability distributions
Dynamic simulation	Dynamic simulation of task sequences
	Dynamic allocation of resources to tasks
	Dynamic invocation of procedures to compute resource utilisation statistics
	Monte Carlo simulation
	Single-threaded, multi threaded and parallel processing
Flexible development environment	Graphical user-interface
	Modular
	Extensible

Extend (Imagine That Inc., San Jose, USA) is a visual, interactive Window-based simulation package that is tailored for a broad range of industries. Models are constructed graphically by dragging and dropping blocks from library windows onto the model worksheet. Data can be entered directly into block dialogs, interactively using controls or read from files as the simulation runs. The block development environment includes a fully featured, compiled, ModL language that allows simulation modellers to add custom functionality. This toolkit combines sophisticated statistical analysis with specialised blocks for processing, batching,

transportation etc to provide a wide variety of modelling opportunities. It offers unlimited hierarchical decomposition and contains features to streamline operations, document procedures, identify bottlenecks and answer questions about capacity, productivity, utilisation etc. Extend Industry Suite v5, an extension of basic Extend, provides an integrated database system, which is necessary for the storage of modelling data.

Extend Industry Suite v5 was found to be the most appropriate software package and was chosen as the simulation package for the implementation of the decision-support tool. The "drag and drop" feature provides a user-friendly interface. ModL is a relatively easy programming language to learn and program due to its similarity with the C language. Extend has a customisable graphical and animated interface that provides a clear visualisation of the steps in the simulation run. This graphical tool offers an unlimited hierarchical decomposition to build complex systems. Microsoft Excel was chosen to provide the database interface, as it is transparent to most users and is compatible with Extend Industry Suite v5.

3.8 TOOL OVERVIEW

Having developed the conceptual framework and selected the software platform, the research carried out to develop the prototype tool is described. In developing the tool the challenge was to represent the declarative and procedural knowledge required in a sufficiently robust manner, so as to enhance the efficiency, maintainability and reusability of the application. All work was implemented in Extend Industry Suite v5 and Microsoft Excel. Since all-necessary building blocks specific to biopharmaceutical drug development are not part of the basic blocks, a number had to be custom built.

The system definitions comprise all the declarative and procedural knowledge for modelling manufacturing operations. The declarative knowledge consists of all the objects, such as tasks and resources, and their class definitions describing their properties. The procedural knowledge enables programmatic control over an application and takes the form of procedures, methods and rules.

The steps to translate the framework into a software tool are as follows:

- Identify the tasks and resources in the development domain
- Create blocks for each task and resources
- Within each task and resource block, provide the procedural information to:
    - Set attributes
    - Perform calculations
    - Assign resources
    - Export output data to database
    - Simulate durations
- Create database in Excel spreadsheet for input and output data
- Establish connection between Extend and the database

The graphical user interface simplifies rapid prototyping of specific cases since it is highly interactive and provides visualisation of the various drug development levels.

3.9 TOOL STRUCTURE

This section describes the main components that were created to model the process of drug development. A graphical user interface is used to represent the activities and resources of the development process. The tool was designed to comprise of four main components (Figure 3.2). They being, the activities in the drug development pathway, the market, resources and the database. Within the tool, each drug is modelled as an item. Once a simulation is started, a drug candidate that is taken into clinical development is taken through the drug development pathway and into the market beginning with Phase I. The resources needed for this process are made available through the resource component of the tool.

Once a drug is in the market component, the activities that take place when a drug enters the market (e.g. sales, manufacture of material and market competition) are simulated. The different attributes and data needed for this simulation process are imported into the modelling blocks from the database. The data that is generated within the tool are then exported into the user interface where further calculations can be performed in order to analyse this data. Next, each of the separate components of the tool is described in detail.

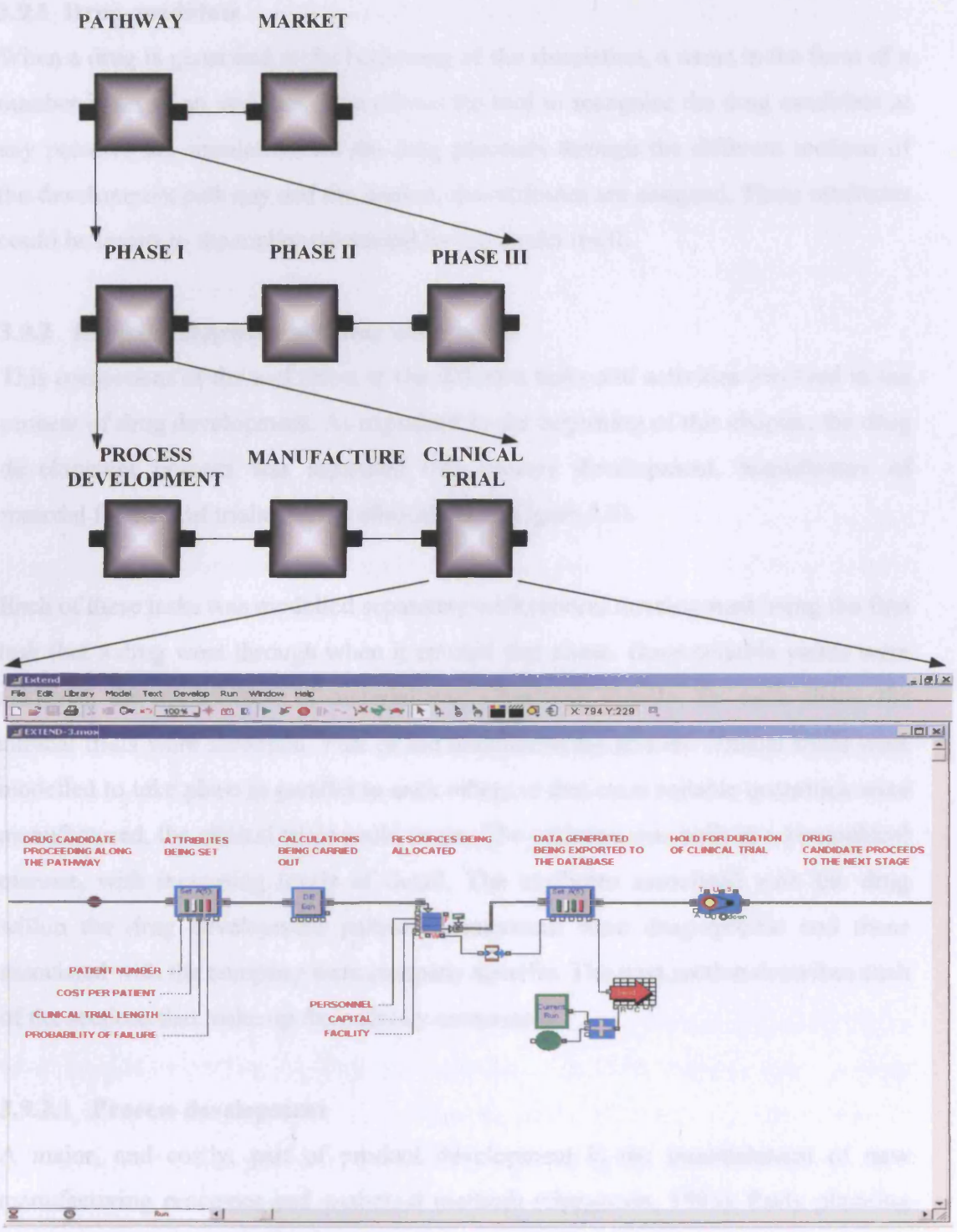


Figure 3.4 Hierarchical structure of the drug development pathway model. By simply clicking on each level, the level below can be accessed. The blocks that are used to simulate the activities of the clinical trials are presented in detail. Changes to the values of the attributes during a simulation can be carried out by clicking on the particular block.

3.9.1 Drug candidate

When a drug is generated at the beginning of the simulation, a name in the form of a number is set as an attribute. This allows the tool to recognise the drug candidate at any point of the simulation. As the drug proceeds through the different sections of the development pathway and the market, the attributes are assigned. These attributes could be inputs to the tool or calculated by the model itself.

3.9.2 Drug development pathway component

This component of the tool refers to the different tasks and activities involved in the process of drug development. As explained in the beginning of this chapter, the drug development process was separated into process development, manufacture of material for clinical trials and the clinical trials (Figure 3.3).

Each of these tasks was modelled separately with process development being the first task that a drug went through when it entered that phase. Once suitable yields were achieved, the manufacture of material was simulated. Finally, for each phase, the clinical trials were modelled. Part of the manufacturing and the clinical trials were modelled to take place in parallel to each other, so that once suitable quantities were manufactured, the clinical trials could begin. The pathway was built in a hierarchical manner, with increasing levels of detail. The attributes associated with the drug within the drug development pathway component were drug-specific and those associated with the company were company specific. The next section describes each of the sections that make up the pathway component.

3.9.2.1 Process development

A major, and costly, part of product development is the establishment of new manufacturing processes and analytical methods (Gregersen, 1995). Early planning of process development activities and the appropriate allocation of resources to the stage of clinical development are key to cost management and meeting clinical trials demands on time. These process development activities were modelled in order to prototype different management and resource allocation strategies.

As the drug candidate enters the process and product development activities the attributes in Table 3.3 are assigned (Figure 3.5). These are estimations based on

similar drugs that have been developed. If such data is not available a set of default data can be used. Alternatively, a range of values with a probability distribution could be assigned.

Table 3.3 Attributes assigned at the process and product development stage

Attributes set for each drug candidate
Number of personnel required for development work
Duration of process development
Estimated cost of development
Target yields

The number of personnel refers to the managers as well as scientists, process development engineers and all other staff. The work carried out during process development has been described in Chapter 2. Once the attributes have been set, the process development work is simulated. The number of personnel required is drawn in from the resource pool that contains the process development personnel. Next, the drug is held within a block for the duration of the process development work. If the number of personnel required is not available, the drug candidate will be held back till the number become available. This waiting time is measured and added onto the total time for development.

The outputs of process development are the total cost and duration of development. These data outputs are then exported to the database. Here, the user will have access to a breakdown of the process development data. The outputs from process development sections from each phase are presented in Table 3.4. The facility in which the process development is carried out was modelled as part of the resource component of the tool and is described separately. The description above is the same for Phase I, II and III. In Phase III, the probability of failure due to economic or technical reasons is included. The simplified schematic in Figure 3.6 provides a summary of the activities taking place within the process development activities.

Table 3.4 Outputs from the process development activity

Output
Waiting time
Total development time
Total cost of process development

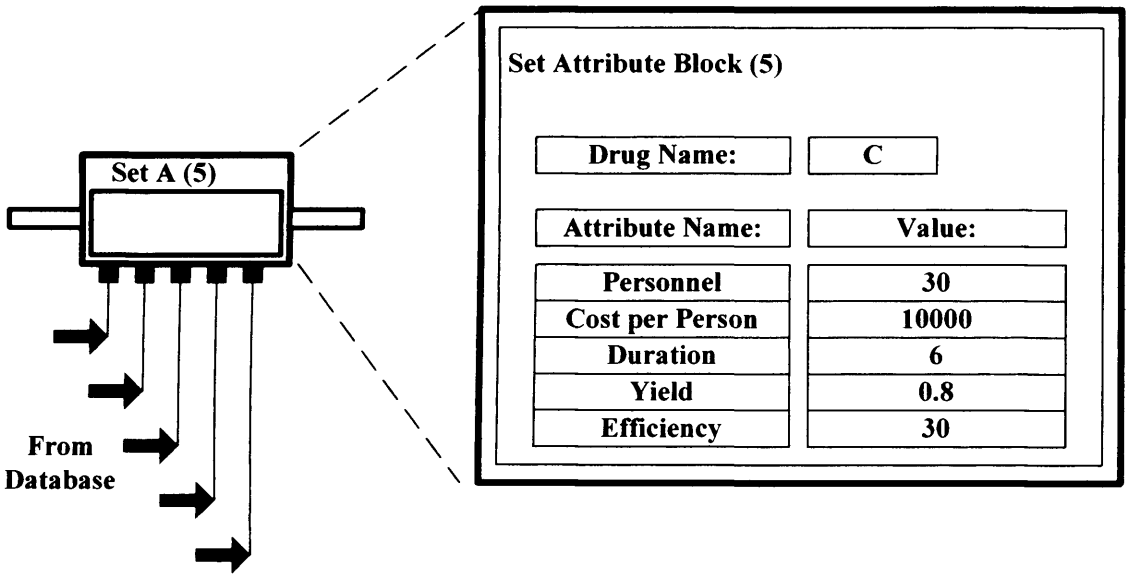


Figure 3.5 Schematic of a 'Set Attribute' block for the process development section. The inputs from the database are imported by 'Receive Data' blocks, which apply the values to the attributes directly. The drug name attribute is used to identify and distinguish between the different drugs.

3.9.2.2 Manufacture

The aim of this part of the tool was to capture the business aspect of the manufacturing process in order to simulate different manufacturing strategies such as outsourcing vs. in-house manufacture. Biopharmaceutical manufacture takes place in batch or semi-continuous mode. The level of detail was limited in order to capture the strategically important cost and risk changes in manufacturing activities of drug candidates for clinical trials.

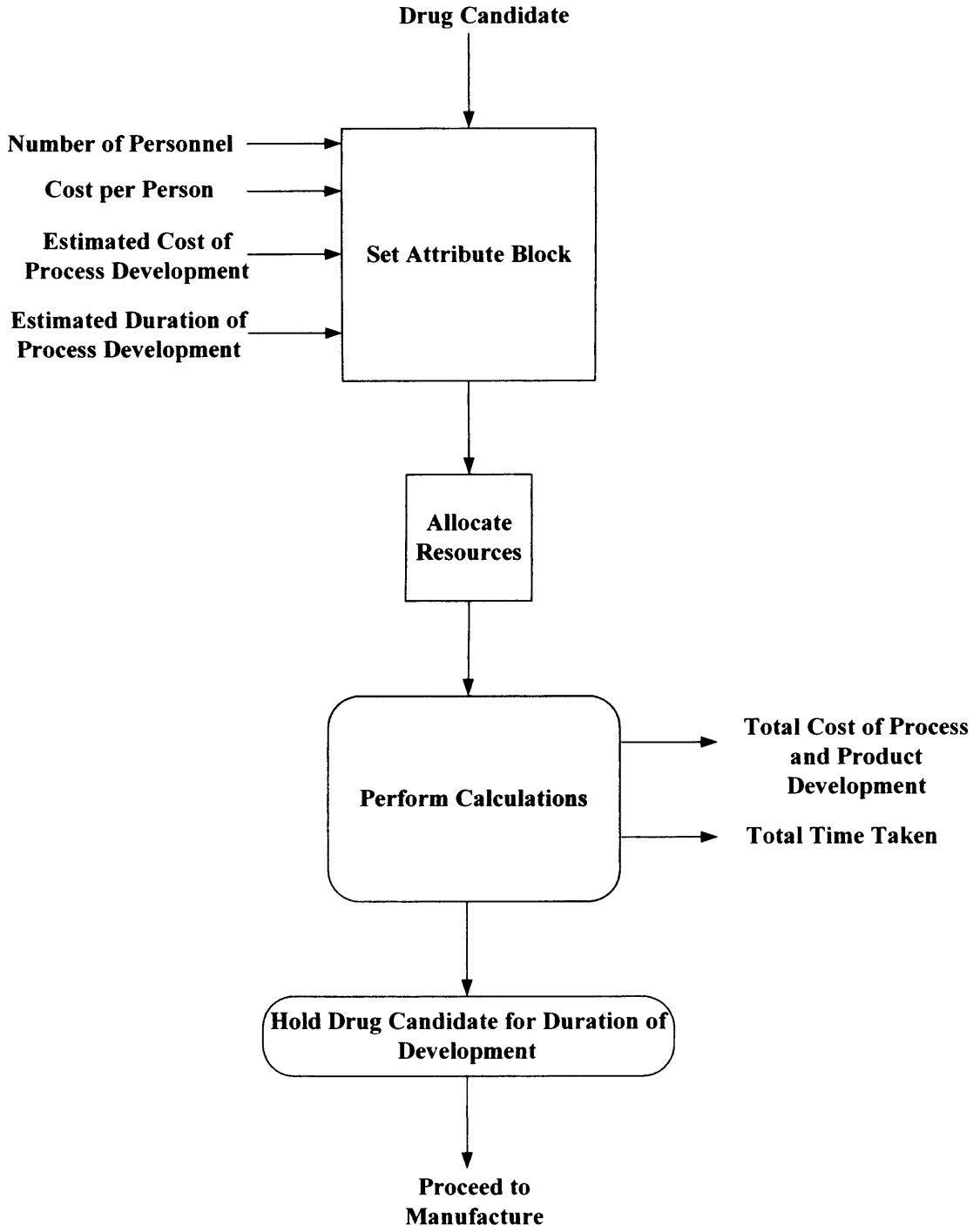


Figure 3.6 The simplified schematic of the process development modelling section of the tool. Basic blocks from Extend were used to build a model of the process development activities.

Once the process development work has been completed the drug candidate will move into manufacturing the material for clinical trials. The facilities for manufacturing were modelled in a flexible manner, in order to change the resources

for each different simulation. These facilities will be described in further detail in the section concerning the resource component of the tool (Section 3.9.4).

The manufacturing process was modelled in two basic stages, the upstream process of protein expression and the downstream process of purification. Once the capacity of the manufacturing facilities (e.g. reactor volume) is defined, the process yields and recovery efficiency attributes from the process and product development section are used to calculate the number of batches and the time for the manufacturing campaign. The availability of the manufacturing personnel and the facilities, both upstream and downstream are used as resource constraints for the manufacturing process. As with the process development, as the drug candidate enters the manufacturing stage, attributes specific for manufacturing are assigned (Table 3.5).

Table 3.5 Attributes assigned for the simulation of the manufacturing process

Attributes assigned to the drug candidate
Manufacturing personnel required
Cost per person
Estimated quantity of drug to be manufactured
Upstream campaign time
Downstream campaign time
Yield
Turnaround time for the facility
Batch cost
Contract negotiation time (for contract manufacturing)

Once the attributes have been set, the drug candidate would move onto the manufacturing block. The manufacturing could be either in-house or contracted out depending on the simulation settings. The default strategy within the tool was set to outsource a drug candidate if the internal facilities were occupied with a different drug. The user has the option of setting the strategy and the level of resources, for example the size of the fermentor or the number of down stream processing facilities available. The tool would then perform the simulations and calculations required. The capability for batch failure and manufacturing delays to occur was incorporated. The outputs for the manufacturing stage are shown in Table 3.6.

Table 3.6 Outputs from the manufacturing stage of the pathway component

Output
Number of batches produced
Waiting time
Total manufacturing time
Total cost of manufacture

As in the process development stage, the data generated are exported to the Excel spreadsheet database for further analysis. If there is a shortage of resources, the waiting time of the drug is measured separately and is included in the total manufacturing time. The drug candidate is then held on within a block for the duration of the manufacture in order to simulate the manufacturing period. This allows the effect of changing resource levels on manufacturing time to be investigated. The manufacturing stage is modelled in this same manner for all three phases.

3.9.2.3 Clinical trials

Once the quantity of material to start the clinical trials has been manufactured the drug development process would move onto the clinical trials. As the drug candidate enters the clinical trials the attributes for clinical trial are assigned initially (Table 3.7). The drug then moves on to simulate the process of clinical trials and calculate the outputs for the stage.

Table 3.7 Attributes assigned for the simulation of the clinical trials

Attributes assigned to the drug candidate
Number of personnel needed for managing the clinical trials
Number of patients per trial
Cost per patient
Clinical trial time
Contracted clinical trial time
Contract cost per patient
Probability of failure at the particular clinical trial

The cost per patient refers to all the expenses involved for the full duration of the clinical trial. This value depends on the disease for which the therapy is being developed, for example, a cancer therapy will need a wide range of tests be performed to monitor the drug's efficacy, while a high blood pressure drug would require far less. The outputs generated for each clinical trial are presented below in Table 3.8. These values are then exported to the database to perform further analysis.

The option of performing the clinical trials in-house or contracted out was incorporated by having two different blocks. The user had the options of setting the strategy that was followed for doing the clinical trials in-house or contracted out. In the default setting within the tool it was set to contract out the drug in the instance where the internal resources (personnel) were occupied with a different clinical trial. If that setting is not applied, the drug candidate will continue to wait until the resources are made available and this waiting time will be measured and added onto the clinical trial time.

Table 3.8 Outputs generated from the clinical trial stage of the pathway component

Outputs from the clinical trial stage
Total cost of the clinical trial
Total duration of the clinical trial

At the end of the clinical trials, the successful drug would pass onto the next phase or if the Phase III trials were completed, the drug would be launched into the market after the regulatory review period. The option of drug failure occurring due to the drug not meeting the expected efficacy and toxicity levels was simulated once the clinical trials were completed. Once a drug fails, the simulation of that particular drug will stop at that position, while the other drugs in the portfolio will continue along the pathway.

3.9.3 Market component of the tool

Drug candidates that complete the development successfully are launched into the market. The many activities that are involved in the sales effort of the drug that has been launched are simulated within this section of the tool. At the beginning of the market simulation, the specific attributes are assigned to the drug (Table 3.9).

Table 3.9 Attributes assigned for the simulation of the market performance

Attributes assigned
Patent length of the drug (years)
Potential patient population
Price per treatment
Marketing cost factor
Sales pattern
Cost of goods

The cost of goods per gram was used to account for the manufacture of material for the market, as is the case in the industry (personal communication, Steve Froud, Lonza Biologics, Slough, UK). Once the development process is over, the patent time left in for the drug is calculated. During this time period, no similar drugs are simulated within the market. The option of applying different sales patterns was made available to the user and this included the possibility of introducing a competitive drug. The marketing cost factor refers to the percentage of the annual revenue reserved for marketing and administrative costs.

3.9.4 Resources component of the tool

Modelling the resources that individual tasks require was achieved by defining a resource pool, which represents a set of available resources and resource queue blocks, which associate a particular resource with a particular task in the simulation model. Access to the resources was made available to all the tasks in each level of the pathway component. The option of prioritising the allocation of resources was incorporated and allowed the user to decide whether to use it or not. Resource usage relationships were then defined for each task so that they could draw upon the associated resource pool to simulate the consumption and renewal of resources, simultaneously constraining the model.

The resources include the personnel, facilities and capital for drug development. Since Extend already had resource and resource queuing blocks, they were customised to be placed in the tool. The resource queuing block, within which drug candidates would await resources, had the ability to calculate the waiting time for

resources and then allocate the resources as soon as they became available. The attributes of the resources were all set to be company specific attributes.

3.9.4.1 Personnel

The personnel were divided into different pools according to the tasks they were to perform. These categories being process development, manufacture of material, management of clinical trials and sales. When a task has to be performed, for e.g. process development work, the demanded number of personnel would be allocated to the drug candidate for the required time period and then returned to the pool after the task has been completed. Within a pool of one type (e.g. process development) there was no further breakdown of personnel into sub-categories, for example biochemical engineers, chemists etc. For each of the human resource pools the attributes assigned were number of people, cost per person and the availability.

3.9.4.2 Facilities

Facilities are required for process development work to be carried out as well as manufacturing of material. For simplicity and flexible operation the facilities were modelled using capacity, cost and availability attributes. For the manufacturing facility an associated fermentor capacity, cost of the facility and whether the facility was available for use or not at any given point of time was specified. The research facilities were associated with a cost. The cost and the depreciation of the facilities were taken into consideration when the overall costing of the drug development process was made. These are presented in Chapter 4. The ability to make additional investments in the facilities was incorporated into the tool. This allowed the user to model facility expansion during a simulation. A maintenance cost was assigned to the facilities for the time period when they were not in use.

3.9.4.3 Capital

The capital refers to the quantity of money available for all the activities. The capital pool is available to pay for the different tasks in the drug development process. Once the task has taken place, the request for payment would be made to the capital resource pool. The drug candidate would not be released until the capital was paid. Once a drug is launched into the market, the revenue generated is paid into the capital pool, enabling the company to perform further work on the drugs that are still

in the development process and require capital. All capital requirements were set to be handled by one capital pool on a first-come-first-served basis. As with other resources, the option of setting priorities for allocation was set up in case the user required doing so. The capital resource pool can be updated at the beginning and at any point of the simulation.

3.9.5 Database component of the tool

The database was used to export inputs into the tool and store the outputs of the tool as well as perform further analysis work. A Microsoft Excel spreadsheet was used as the database. Data import and export blocks provided by Extend allow data to be transferred between the tool and Excel spreadsheets. Before each simulation the inputs for that particular simulation is entered into the Excel spreadsheet. As the simulation is progressing, the outputs generated are exported into the database.

3.10 Representing uncertainties in parameter values

As explained in Chapter 2, much uncertainty and risk is present in the process of developing as well as marketing a drug. Uncertainties in drug development are associated with factors such as yields, costs, durations, clinical success, price and patient population. Traditional project appraisals tend to be deterministic where uncertainties are not dealt with explicitly. By incorporating the effects of risk, the functionality of the tool was enhanced as it enabled the certainty associated with output measures to be expressed. Once the key uncertainties are identified, probability distributions can be assigned in order to reflect the risk of a proposed strategy. Historical data and expert opinion was used to identify suitable distributions. Monte Carlo simulation technique is used to determine resulting frequency distributions of the output measures.

Extend allows a wide variety of distributions, both continuous as well as discrete to be applied (Figure 3.7). For each of the distributions, arguments (e.g. mean and standard deviation for normal distribution) are set before the simulation starts. This allowed the possibility of setting the type of distribution that best described each parameter during simulation studies. For example, the sales pattern could be described using a normal distribution whereas the variation of the cost of process development could be specified using a triangular distribution. Probability

descriptions of input variables and Monte Carlo sampling together provide a practical method of finding the distribution of the desired output given the various random and deterministic input variables (Farid *et* al., 2001; Coates and Kuhl, 2003).

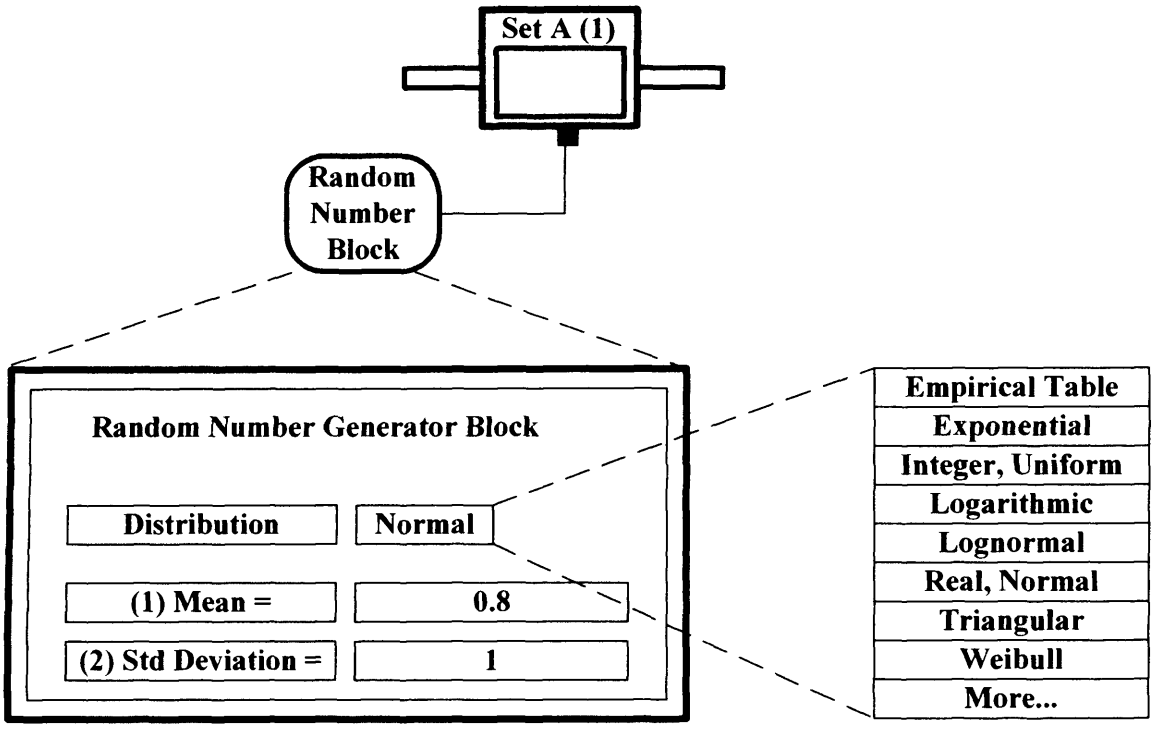


Figure 3.7 Schematic representation of the application of distribution probabilities to parameters. The distribution is applied via a 'Set Attribute' block.

3.11 Conclusions

The research and programming decisions made in order to construct a prototype tool to model the process of drug development have been presented. The modelling approach developed and adopted in this thesis allows modellers to capture effectively both the risks and rewards in the process of biopharmaceutical drug development process. The process of building the simulation model allows better understanding of the process of drug development. During data gathering, the areas in which high uncertainty exists can easily be identified. This process brings together personnel from different areas of expertise such as process development, manufacturing, clinicians, accountants and all levels of management. The simulation results can then be used to build consensus amongst decision-makers.

The framework allows alternative management strategies to be prototyped before being implemented in the process of drug development. The hierarchical framework is modular and extensible allowing further levels of detail to be added as required. Hence, users interested in obtaining an overview of the key performance metrics in the process may simply model the higher-level activities. Alternatively if a user requires modelling only the process development activities, then the simulations could be run using only that section of the tool. As with any applications package, the tool can evolve as new problem features become apparent. The next chapter describes the functionality of the prototype tool and the data that is been used as default data.

CHAPTER 4

OPERATION OF THE TOOL

4.1 INTRODUCTION

The previous chapter presented the design and implementation of the prototype tool to model the biopharmaceutical drug development process. This chapter describes the different ways in which the tool can be applied to assist decision-making in the process of drug development. The method of operating the tool and the default data used are also discussed. Given the level of uncertainty and risk in drug development, the ability to prototype different strategies for drug development will help to contain cost and minimise losses due to drug failure at different stages in the development pathway.

A tool such as the one developed in this thesis and that combines the biopharmaceutical drug development activities (e.g. process development, manufacturing and the clinical trials etc...) with the resource flows (e.g. cash, facilities, personnel etc...) has not been presented in the literature.

The ability to model and evaluate the impact of process and business options within a company could greatly enhance decision-making and improve the economics of new drug development (Karri *et al.,* 2001). A typical example might be that the early planning of development tasks and the appropriate allocation of resources will help the company to identify resource bottlenecks and act upon them early.

The utility of the tool is first discussed in general in Section 4.2. Next, the steps involved in setting up a simulation and running it is discussed along with the key inputs and outputs of the tool (Section 4.3). This is followed by the description of the data that is being used for the case studies in this thesis in Section 4.4. The chapter ends with a set of conclusions in Section 4.5.

4.2 TOOL UTILITY

As described in Chapters 1 and 2, the process of drug development is a costly and lengthy one where failure may occur at any point. The developed tool has the blocks required to simulate the process of drug development at differing levels of detail. A tool such as this one could be utilised to explore the different strategies used in managing the development process of biopharmaceuticals. The main features of the tool include the ability to:

- Prototype the biopharmaceutical drug development process at strategic, tactical and operational levels;
- Identify the key parameters and business issues in the drug development process and model them;
- Evaluate the risk and reward of different strategies in the process of drug development by simulation and measuring specific outputs from the model;
- Select the optimum portfolio for a small to medium-sized company, operating under a given level of resources.

The different strategies the simulation model is able to address are:

- Resource decisions – e.g. how many process development staff should be deployed and for how long for the process and product development activities to be completed;
- Scenario analysis – e.g. what should be the best price for the drug and what level of patient population should be captured in order to break-even;
- What is the best manufacturing strategy – e.g. should an investment be made on a facility for in-house production and if so when;
- Product portfolio selection – e.g. for a given level of resources available to the company what are the products that should be taken in for clinical development.

In Chapter 5, the application of the tool to investigate resource allocation and scenario analysis is presented. Also included in the same chapter is a case study in which two different strategies regarding the manufacture of material is prototyped. Chapter 6 describes the application of the tool to select the optimal portfolio from a set of available drug candidates under resource constraints. The next section describes the steps involved in operating the tool.

4.3 USING THE PROTOTYPE TOOL

4.3.1 Simulation process

Whenever a simulation is run, the simulation clock advances with the completion of each task and the simulation model is animated to enable the user to view what is happening at any point in time. The executive block keeps track of the simulation time. The graphical user interface of the tool is shown in Figure 4.1 This functions as the main operating window of the tool. Attributes of the tasks and resources are initialised through the use of input blocks.

During a simulation run, the model is animated to enable the user to view the occurrence of events at any given point in time. Animation features enable the visualisation of the flow of items (for e.g. drug candidate) throughout the simulation run and aids in the de-bugging process for the developer. The use of discrete event modelling gives the capability to view the time-based behaviour of the system and makes it possible to track the values of time-dependent parameters such as cost and resource usage (Lim *et al.*, 2004).

4.3.2 Decision points

The generic model was set up with a standard number of decision points along the drug development pathway. Each decision point provides an overview of the issues involved in a decision and the options available. When running simulations, the user had the option of making modifications according to the case study. Figures 4.3 to 4.6 show the main decisions and the options available for a drug proceeding along the pathway.

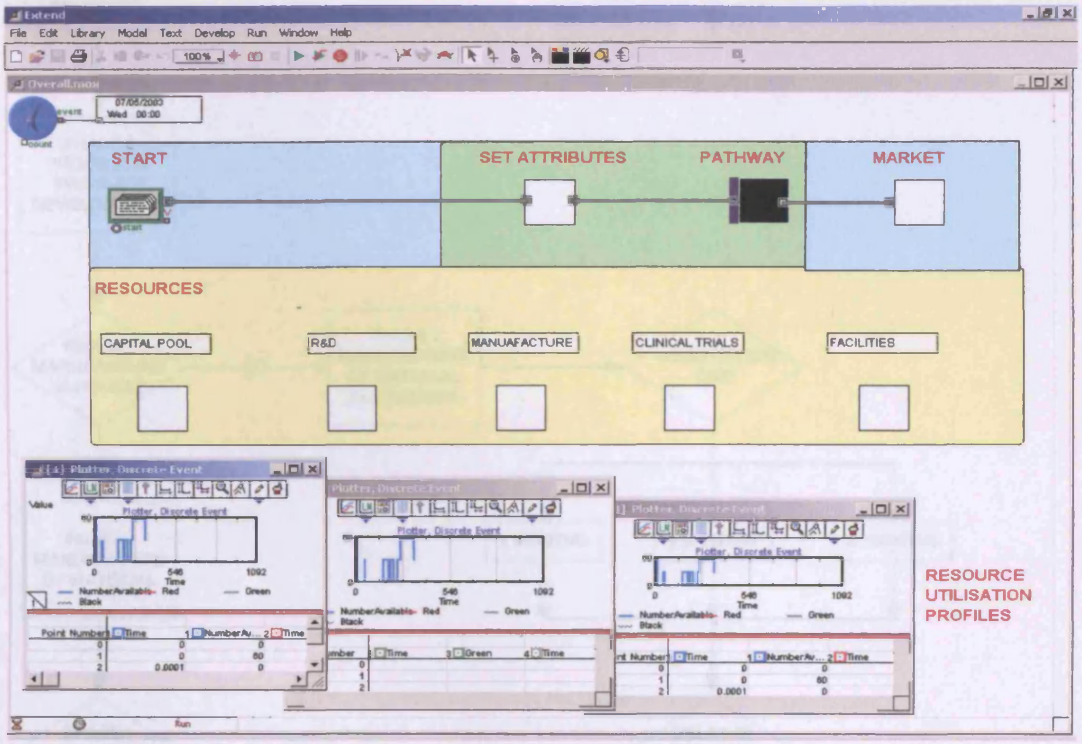


Figure 4.1 The graphical user interface. The executive block is located at the top left hand corner of the interface. The active blocks (for example the Pathway block for this simulation) are highlighted during the simulation.

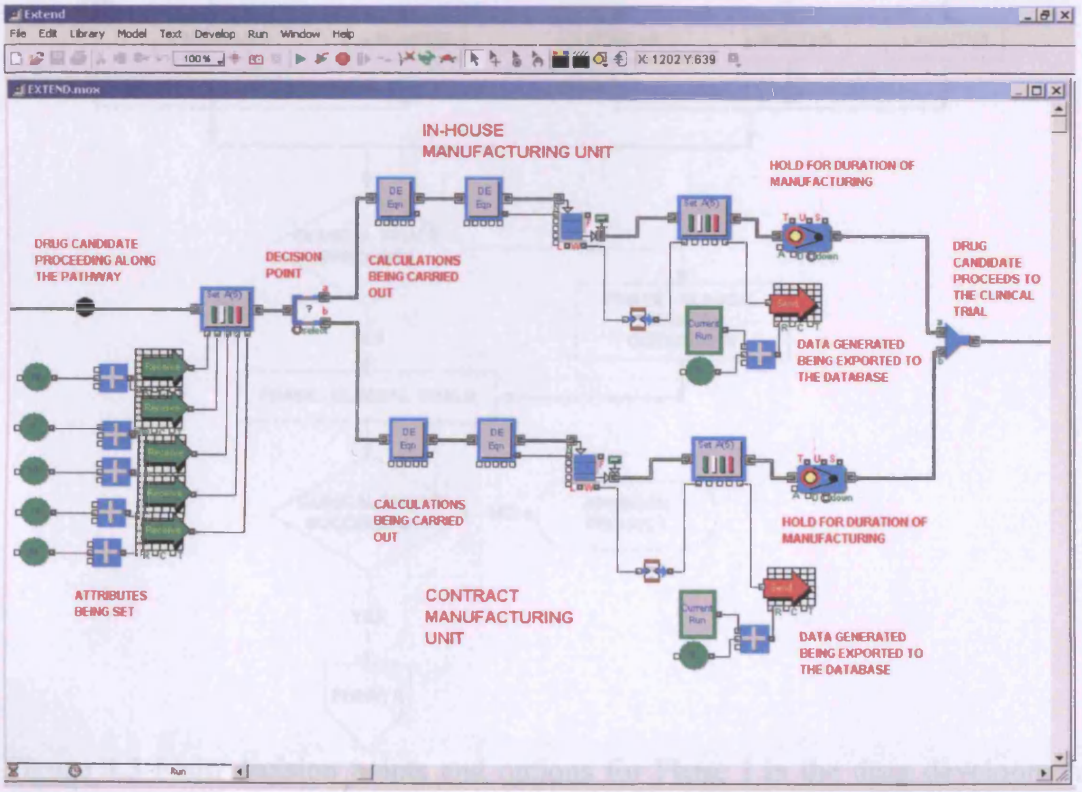


Figure 4.2 Layout of the blocks of the manufacturing options. The decision to manufacture the material in-house or contract out is made at the decision point.

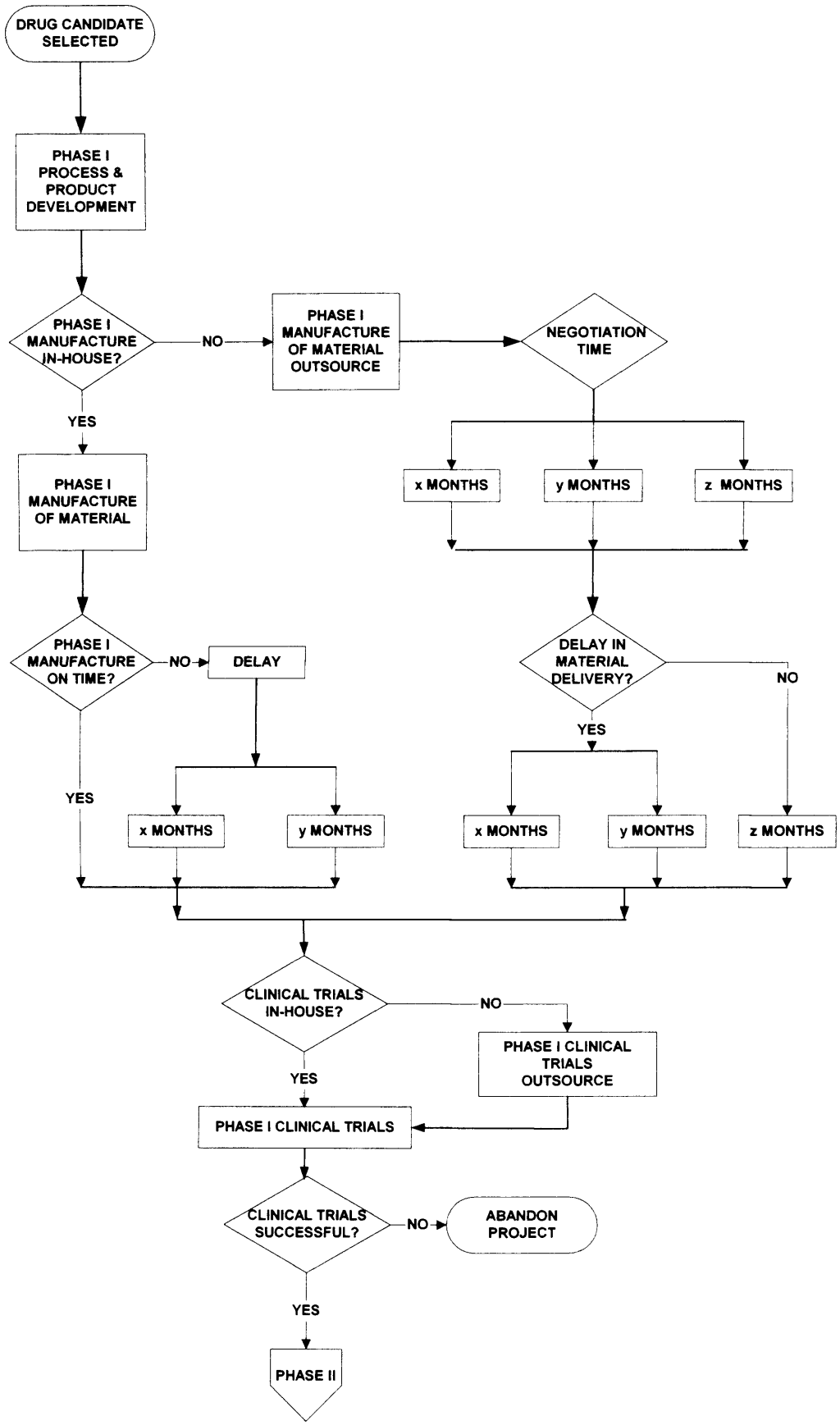


Figure 4.3 Main decision points and options for Phase I in the drug development pathway. Probability distributions assigned decide which of the values, x, y or z is selected for each simulation run.

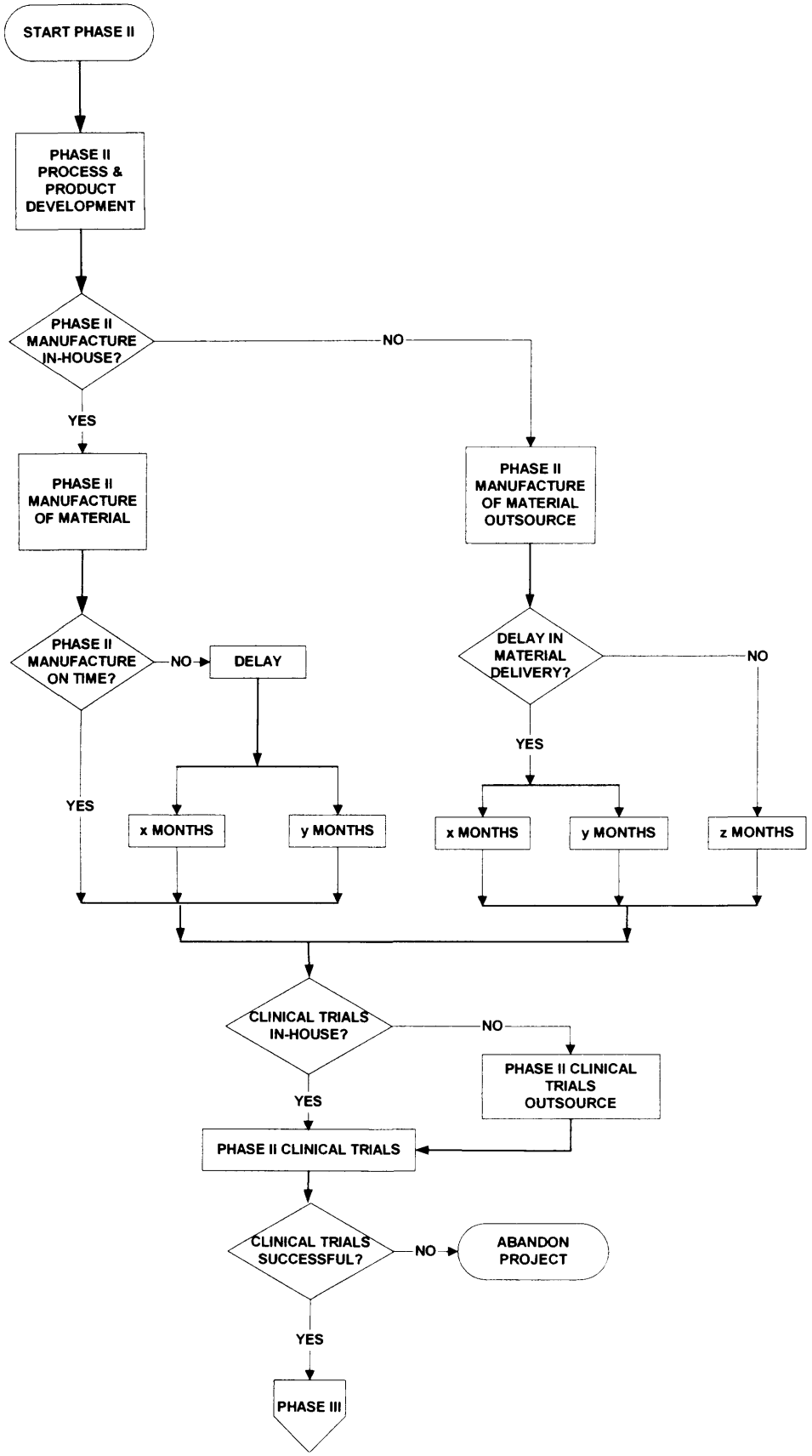


Figure 4.4 Key decision points of Phase II in the drug development pathway. The user has the options of changing the number of options or the values (x, y and z) according to the case study. For a deterministic simulation, the default values entered will be used.

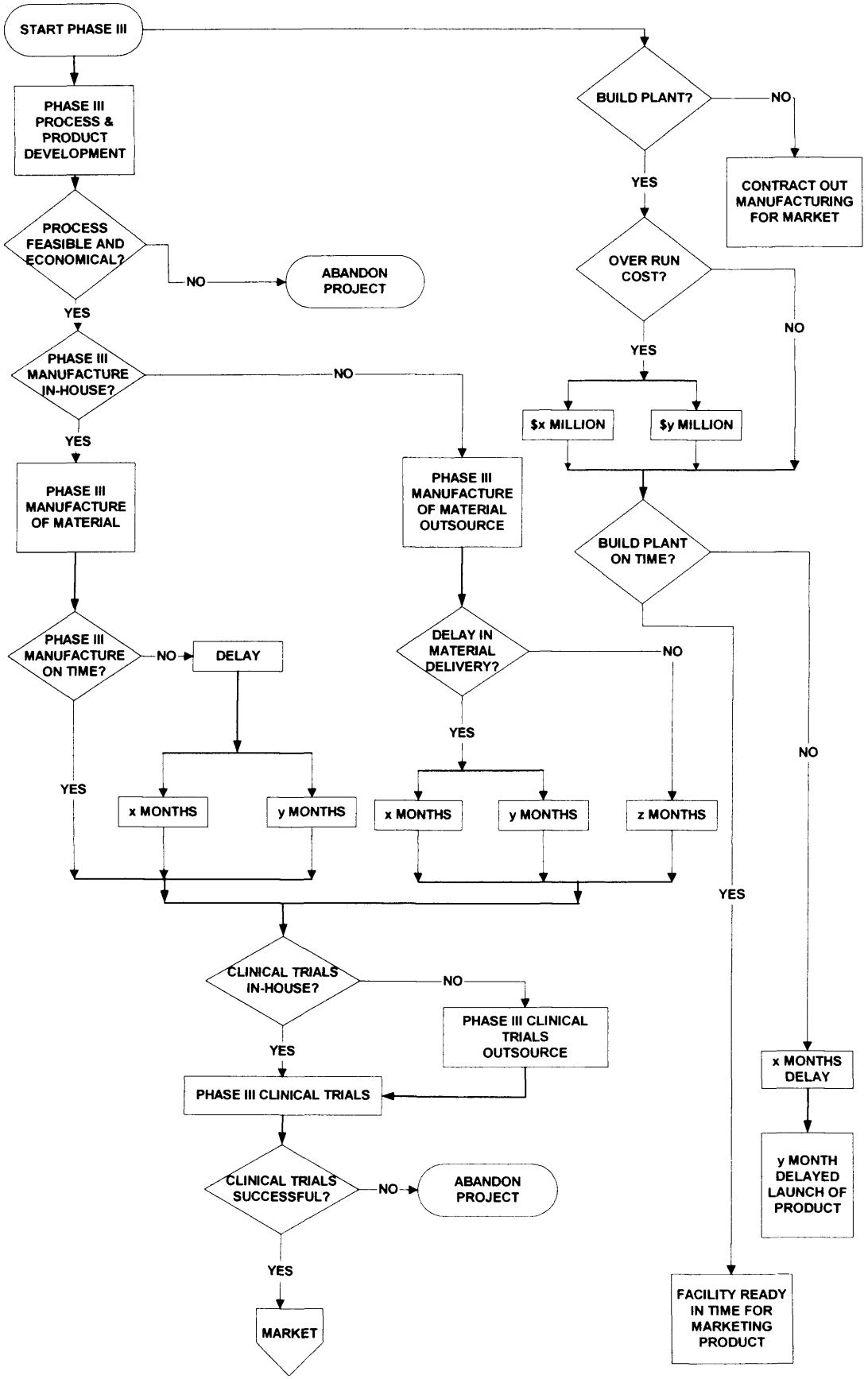


Figure 4.5 Key decision points of Phase III in the drug development pathway. The decision regarding whether to build a facility is included in the options available as it is at this stage that this question has to be addressed by the decision-makers.

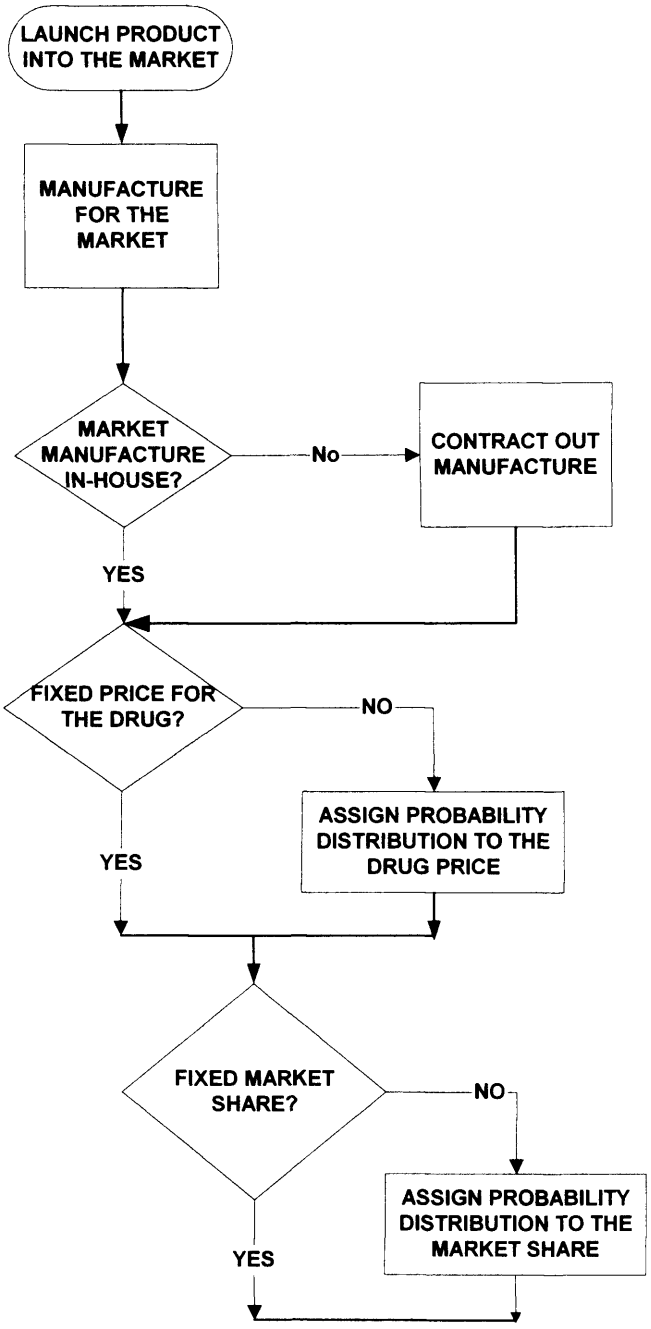


Figure 4.6 Decision points in launching a drug in the market after successful completion of Phase III. By assigning probability distributions and running Monte Carlo simulations the uncertainty in the drug pricing and the market share captured was modelled.

4.3.3 Inputs and outputs of the model

The key inputs to and outputs from the tool are discussed below and summarised in Figure 4.7. As described in Chapter 3, an Excel spreadsheet was used to input data as well as collect the data generated by the tool and performs further analysis. Setting up a simulation of a drug development process involves specifying the resources of

the company and the estimated attributes of the drug candidate. Factors and rates such as taxes that are to be used in calculating various profitability indicators (e.g. revenue, NPV) have then to be specified. When performing Monte Carlo simulations the probability distributions have to be defined. These could be selected from a default Extend file or be defined by the user. Next, the user has to define the strategy that is being applied. For example, the decision to manufacture the material in-house or to contract out has to be set accordingly (Figure 4.2).

After a particular case is set up the impact of different development strategies on the value of the portfolio of drugs can be assessed. The key outputs are the cost and time values of different tasks and the net present value (NPV) of the portfolio (Figure 4.7). All the data that is generated during a simulation are held in separate categories according to the point of origination. For example, the data regarding Phase I development is kept separate to Phase I manufacturing data. These values are then added to give totals for each activity (e.g. total development cost across the pathway) and phase (e.g. total manufacturing cost for Phase I). Calculations to perform further analysis on the outputs of the tool were carried out on the Excel spreadsheet receiving the initial information. Figures 4.8 and 4.9 present the user interface for the inputs and outputs of the model.

An example of one of the outputs of the application is the utilisation of the process development personnel over a selected period of time (Figure 4.10). These utilisation figures can be used to compare the demands on resources under different strategies or for different portfolios of drugs. This will lead to identifying strategies that maximise resource utilisation to improve productivity and reduce the time to market. One of the key outputs of the model was the net present value (NPV) of the portfolio for each year of operation. The calculation steps and the assumptions for the NPV calculation are presented in Section 4.4.2.

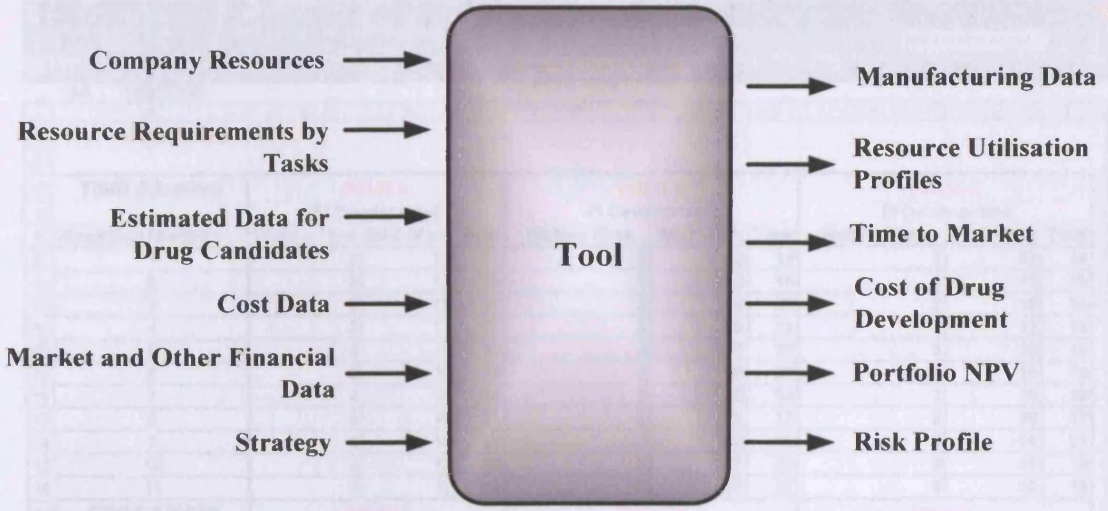


Figure 4.7 Inputs to and outputs from the tool. The key inputs are the tasks, resources, costs and strategy. The key performance measures are cost, time to market, resource use profiles and portfolio NPV.

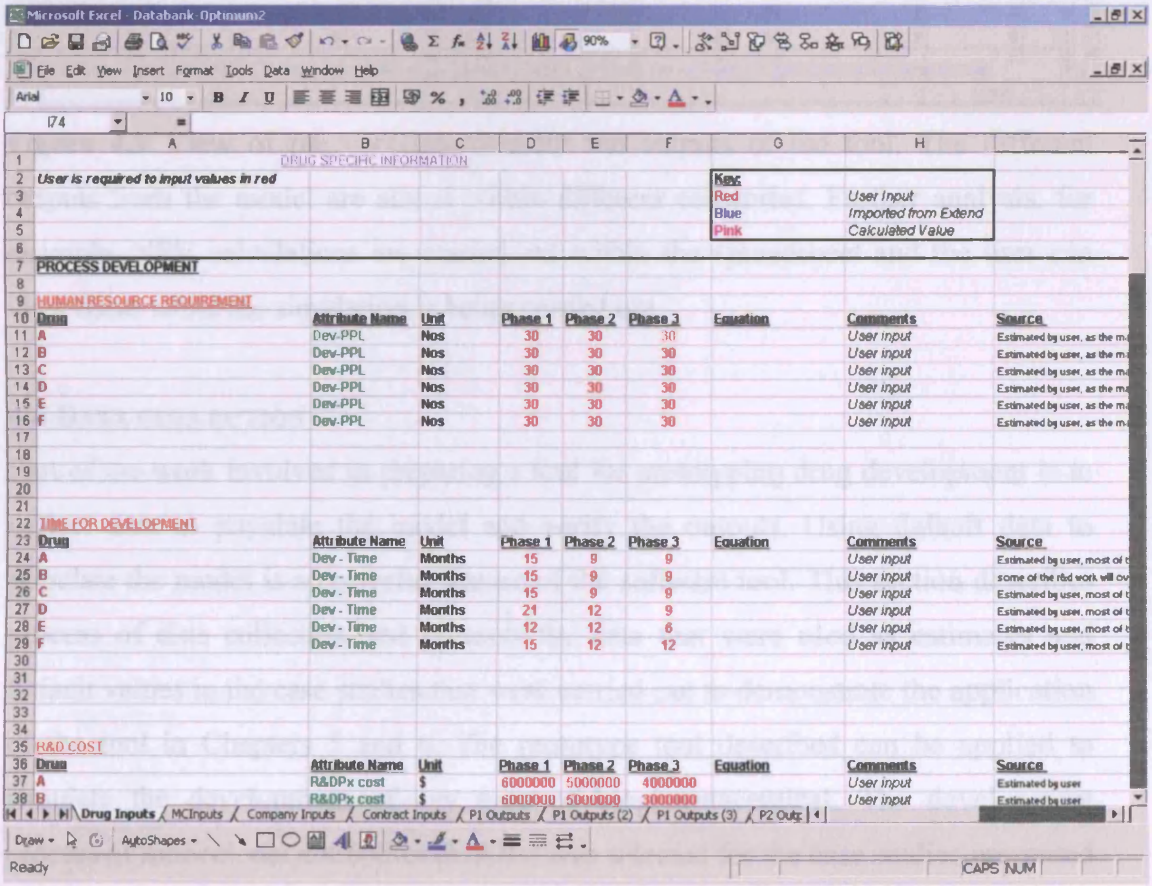
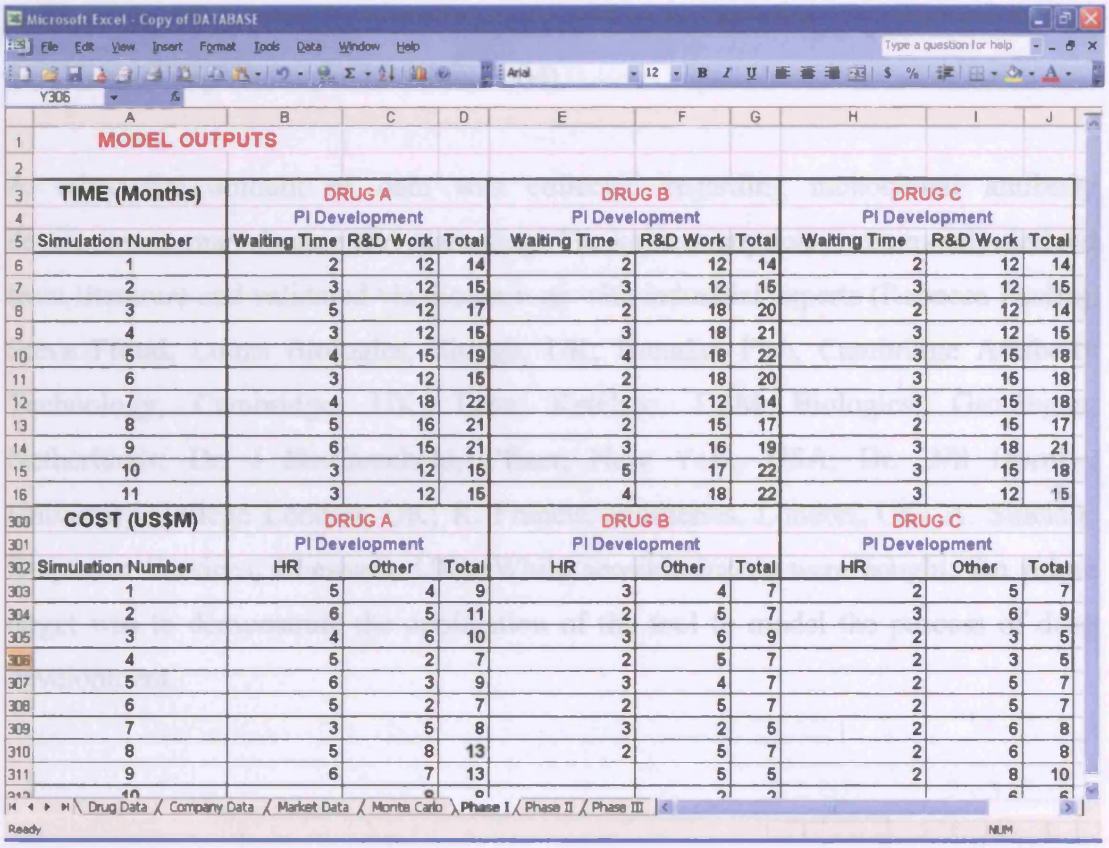


Figure 4.8 View of the user interface to input estimated values of drug candidates, the company resources and market data. An Excel spreadsheet was used as the user interface for data input and output.



Microsoft Excel - Copy of DATABASE

MODEL OUTPUTS

TIME (Months)	DRUG A PI Development			DRUG B PI Development			DRUG C PI Development		
Simulation Number	Waiting Time	R&D Work	Total	Waiting Time	R&D Work	Total	Waiting Time	R&D Work	Total
1	2	12	14	2	12	14	2	12	14
2	3	12	15	3	12	15	3	12	15
3	5	12	17	2	18	20	2	12	14
4	3	12	15	3	18	21	3	12	15
5	4	15	19	4	18	22	3	15	18
6	3	12	15	2	18	20	3	15	18
7	4	18	22	2	12	14	3	15	18
8	5	16	21	2	15	17	2	15	17
9	6	15	21	3	16	19	3	18	21
10	3	12	15	5	17	22	3	15	18
11	3	12	15	4	18	22	3	12	15

COST (US$M)	DRUG A PI Development			DRUG B PI Development			DRUG C PI Development		
Simulation Number	HR	Other	Total	HR	Other	Total	HR	Other	Total
1	5	4	9	3	4	7	2	5	7
2	6	5	11	2	5	7	3	6	9
3	4	6	10	3	6	9	2	3	5
4	5	2	7	2	5	7	2	3	5
5	6	3	9	3	4	7	2	5	7
6	5	2	7	2	5	7	2	5	7
7	3	5	8	3	2	5	2	6	8
8	5	8	13	2	5	7	2	6	8
9	6	7	13		5	5	2	8	10

Drug Data / Company Data / Market Data / Monte Carlo / Phase I / Phase II / Phase III

Ready NUM

Figure 4.9 View of the user interface for the outputs of the tool. The different outputs from the model are stored within different categories. Further analysis, for example, NPV calculations are carried out within the spreadsheet and the user can view these while the simulation is being carried out.

4.4 DATA COLLECTION

Part of the work involved in preparing a tool for prototyping drug development is to collect data to populate the model and verify the outputs. Using default data to populate the model is a powerful feature of the software tool. This section describes process of data collection and presents the data that were used as estimates and default values in the case studies that were carried out to demonstrate the application of the tool in Chapters 5 and 6. The prototype tool described can be applied to simulate the development of any type of biopharmaceutical. The development process of monoclonal antibodies (MABs) was selected for the case studies presented in this thesis. Between 2001 and 2002, the value of the global therapeutic MAB market grew by 37% to US$ 5.4 billion and to date, 17 therapeutic MABs have been approved by the US FDA with 132 more products currently in clinical development (Reichert and Pavlou, 2004). The global market is projected to increase to US$ 16.7

billion by the year 2008 with two major approval waves being expected during the next five years (Reichert and Pavlou, 2004).

A substantial amount of data was collected regarding monoclonal antibody development, manufacture and marketing. The key assumptions were mostly derived from literature and validated via discussions with industrial experts (Rebecca Paulraj, Steve Froud, Lonza Biologics, Slough, UK; Brendan Fish, Cambridge Antibody Technology, Cambridge, UK; Peter Ketelaar, DSM Biologics, Groningen, Netherlands; Dr. J Hettiarachchi, Pfizer, New York, USA; Dr. Bill Hornby, University College London, UK; R. Francis, Protherics, London, UK; A. Sinclair, Biopharm Services, Chesham, UK). While sensible inputs were sought, the prime target was to demonstrate the application of the tool to model the process of drug development.

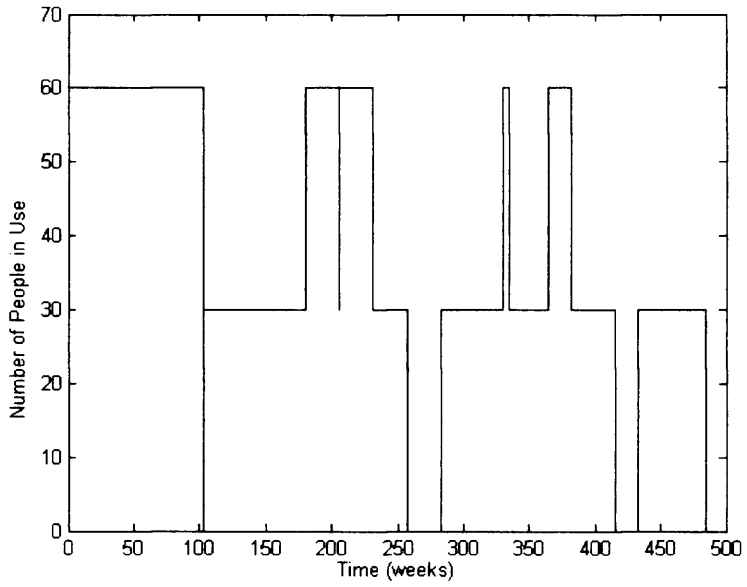


Figure 4.10 Example of a key output of the tool, resource utilisation profile. This particular example illustrates the number of people required during process development of a drug portfolio, where peaks and bottlenecks can be identified for resource allocation planning.

4.4.1 Input data for case studies

This section presents the data that has been used as inputs for case studies in Chapters 5 and 6. A six-drug candidate portfolio was assembled with the information

gathered. A portfolio of three drug candidates is used in Chapter 5, while the full portfolio of six drug candidates is featured in the Chapter 6 case study. Any changes to the inputs made, such as assigning distributions in place of point estimations have been highlighted and described at the point of doing so within each of the case studies.

4.4.1.1 The portfolio

The drug portfolio consisted of six monoclonal antibodies, which were different to each other in type and therapeutic area (Tables 4.1 and 4.2). The drug-specific attributes for the 6 antibodies were based on historical data for commercial antibodies (Farid, 2001). These drugs have been modelled as breakthrough drugs in their respective therapeutic areas.

Table 4.1 Description of the drugs in the portfolio (Farid, 2001)

Drug	Typical cumulative dose/patient (mg)	Typical price/ patient/ treatment ($)	Typical unit selling price ($/g)	Potential annual US market (# patients)	Potential annual US demand (kg)
A	30	1,690	56,300	309,600	9
B	5,740	33,350	5,800	12,800	73
C	1,050	7,590	7,200	54,000	57
D	3000	15,000	5,200	68,000	205
E	70	4,200	60,000	7,300	0.5
F	40	3,160	79,000	15,400	1

Table 4.2 Drug type and therapeutic category (Farid, 2001)

Drug	MAB type	Therapeutic area
A	Chimeric	Clot prevention in PTCA*
B	Humanised	Breast cancer
C	Chimeric	Crohn's disease
D	Chimeric	B-cell non-Hodgkin's lymphoma
E	Murine	Organ transplant
F	Chimeric	Organ transplant

*PTCA - Percutaneous Transluminal Coronary Angioplasty

4.4.1.2 Company

As described earlier the company that was used for this case study was modelled as a small to medium scale company that had its own defined level of resources and manufacturing facilities (Table 4.3).

Table 4.3 Company attributes modelled and their values

Attribute	Value
Capital available ($)	900, 000, 000
Patent life (years)	20
Investment in facility ($)	13, 000, 000
Personnel available for development work	60
Personnel available for manufacture	50
Personnel available for clinical trials	50
Cost per person per month ($)	10,000
Fermentation capacity (1) (L)	12,000L
Fermentation capacity (2) (L)	600L
Cost per batch (PI) ($)	2,000,000
Cost per batch (PII, PIII) ($)	1,500,000
Cost per gram (market production) (US$ per gram)	1,500

Along with the above data the different tasks, resource requirements and the expected timelines for each of these drugs in the development process were then defined within the database. A cost of US$ 6.7 million was assigned to each drug to account for discovery and pre-clinical phases (Myers and Howe, 1997).

The costs of manufacturing (cost per batch and cost per gram) were estimated through discussions with industrial experts (personal communication Rebecca Paulraj; Steve Froud, Lonza Biologics, Slough, UK; Peter Ketelaar, DSM Biologics, Groningen, Netherlands). The investment for the facility was determined through a method suggested by an industrial expert (personal communication, Vaughan Thomas, SciTech Engineering, Guildford, UK).

Cost of facility (US$ million) = fermentation capacity (L)* 0.0017 + 10.79

4.4.1.3 Process development

All three monoclonal antibodies were manufactured using a mammalian cell based process. The development work therefore would involve:

- Establishment of the cell line and characterisation.
- Process development and validation.
- Documentation etc...

The research and development personnel and the facilities have to be allocated to each candidate according to its demand. Where specific data was not available, default data was used and these were kept the same for all the drug candidates for the case study in Chapter 5. In the Chapter 6 different resource requirements were assigned to the six drug candidates. The manner in which these changes were applied is described in Chapter 6 and the data used is presented in Appendix 1.

Table 4.4 Resource requirements and time taken for process and product development for the three phases in drug development

Number of personnel required per drug			Time taken (months)			Cost (US$ million)		
PI	**PII**	**PIII**	**PI**	**PII**	**PIII**	**PI**	**PII**	**PIII**
30	30	30	24	12	12	3	4	5

4.4.1.4 Manufacture of material for clinical trials

a) In-house manufacture

The resource requirement for the manufacture of the drugs within the portfolio is presented next. The production was modelled as a batch process. Again the data was changed for the Chapter 6 case study.

Table 4.5 Manufacturing data for the three monoclonal antibodies during development phases

Drug	Number of personnel required			Quantity required (g)			Mass per batch (g/batch)*		
	PI	PII	PIII	PI	PII	PIII	PI	PII	PIII
A	30	30	30	10	300	1,000	96	300	630
B	30	30	30	300	650	4,000	192	600	1,260
C	30	30	30	10	300	2,500	96	300	630
D	30	30	30	50	470	450	96	300	630
E	30	30	30	1	5	19	96	300	630
F	30	30	30	5	8	15	96	300	630

The mass per batch values were based on the company using a fermentor with a capacity of 600 L for all the drugs except drug B. As drug 2 required products in higher quantities a fermenter of 1200 L capacity was used. The assumptions that were used to calculate the mass per batch are presented in Table 4.6.

Table 4.6 Assumptions for calculating the mass per batch for the three phases

Phase	Titre (g/L)	Yield (%)
P I	0.4	40
P II	1	50
P III	1.5	60

b) Contract manufacturing organisation

The activities of the contract-manufacturing organisation (CMO) were modelled to allow the company to outsource some of the development work and the manufacturing of material for the clinical trials and the market. The cost and time data regarding the manufacturing of material through a CMO (Table 4.7) were compiled from literature (Nicholson and Latham, 1994; Seaver, 1995) and through discussions with industrialists (personal communication Rebecca Paulraj; Steve Froud, Lonza Biologics, Slough, UK; Peter Ketelaar, DSM Biologics, Groningen, Netherlands).

Table 4.7 Attributes and values for the contract-manufacturing organisation

Attribute	Value
Negotiation time (months)	3
Cost per batch (PI, PII, PIII) ($)	970,000
Cost per gram (market production) ($/gram)	2,700
Batch time (PI, PII, PIII) (months)	2
Development cost (PI) ($)	960,000
Development cost (PII) ($)	150,000
Development cost (PIII) ($)	150,000

4.4.1.5) Clinical trial inputs

a) In-house clinical trials

The estimates of the resource requirement for the clinical trials at each phase are presented next. Default data was used for the cost and the number of personnel needed to mange the clinical trials. The number of patients was collected from the public domain (e.g. http://www.gene.com/gene/pipeline/trials/) and a database maintained at UCL. Default values were used for the clinical trial length values, which were estimated from literature (DiMasi, 2003; Stewart *et al.*, 2001) and validated through conversations with industrial experts (personal communication with Rebecca Paulraj, Steve Froud, Lonza Biologics, Slough, UK; Dr. J Hettiarachchi, Pfizer, New York, USA). An average value of 6.5 months was included in the Phase III clinical trials to account for the approval time (Reichert, 2000).

Table 4.8 Clinical trial data used for the simulations

Drug	Number of personnel required			Number of patients			Cost per patient ($/patient)		
	PI	PII	PIII	PI	PII	PIII	PI	PII	PIII
A	40	40	40	79	56	1,300	30,000	50,000	60,000
B	40	40	40	120	82	2,700	30,000	50,000	60,000
C	40	40	40	10	152	2,300	30,000	50,000	60,000
D	40	40	40	35	114	3200	30,000	50,000	60,000
E	40	40	40	8	33	1500	30,000	50,000	60,000
F	40	40	40	105	200	2000	30,000	50,000	60,000

Table 4.9 Clinical trial durations

Clinical trial duration (months)		
PI	**PII**	**PIII**
12	18	24

b) Contract research organisation

The activities of the contract research organisation (CRO) were modelled to allow the company to contract out the clinical trials if required. The costs include that of the physicians, the analysts and the tests needed to conduct the trials. These were compiled through literature (DiMasi *et al.*, 2003) and discussions with industrial experts (Rebecca Paulraj, Lonza Biologics, Slough, UK; Dr. Bill Hornby, University College London, UK; Dr. J. Hettiarachchi, Pfizer, New York, USA). The durations were kept the same as the in-house values.

Table 4.10 Clinical trial cost estimations

Attribute	Phase I	Phase II	Phase III
Cost per patient ($)	30,000	70,000	70,000

4.4.1.6) Failure at clinical trials

One of the biggest practical problems in applying decision analysis is that of estimating probabilities of success (Senn, 1998). The probability for failure at clinical trials was based on data published by Reichert (2001). The rates of failure due to technical reasons were changed according to the case study and these are presented within the sections that describe the respective case studies.

Table 4.11 Phase transition probabilities for MABs (Reichert, 2001)

Monoclonal antibody type	Phase I to II (%)	Phase II to III (%)	Phase III to Review (%)	Review to Approval (%)
Murine Mabs	77	52	45	33
Chimeric Mabs	86	40	80	100
Humanized Mabs	84	72	75	100
Average	82.3	54.7	66.7	77.7

4.4.1.7 Market

Once the drug enters the market, the tool simulates its production for the market and the sales pattern. The patient population data shown in Table 4.1 was used to simulate the market data. The sales pattern shown in Figure 4.11 was applied to all six drugs as the default setting. The six drug candidates used in the case studies were modelled as breakthrough drugs in each of their therapeutic area. Stonebraker (2002) makes an estimation that a new therapeutic agent in a breakthrough market can command 70% – 95% of the market at its peak share. Therefore the peak share for the drugs when they made it to the market was set at 80% (Figure 4.11).

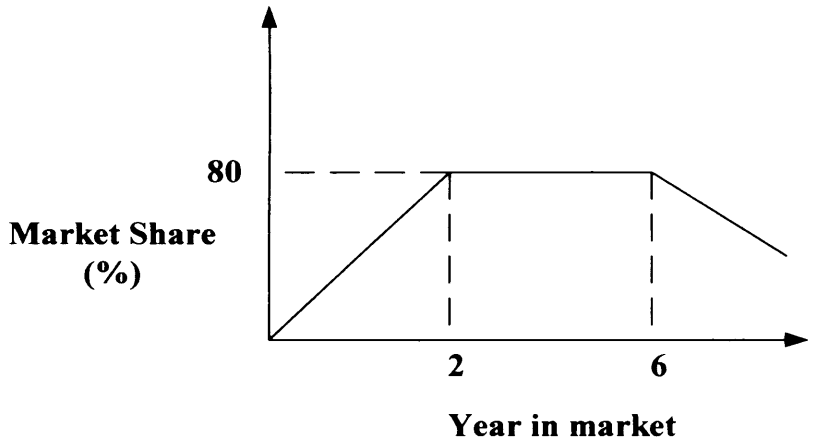


Figure 4.11 Sales pattern applied to each drug once in the market (Myers and Howe, 1997; Stonebraker, 2002).

4.4.2 Net present value

One of the key outputs of the tool was the net present value (NPV) of the portfolio (Table 4.12). A depreciation rate of 11% was used for the NPV calculations (DiMasi *et al.*, 2003). The tax was set at 33% and the discount factor (r) was set at 9% (Myers and Howe, 1997). At the end of each year the model will output the year's expenses and revenues in order for the NPV calculation for that year to be performed. All expenses regarding building new facilities were taken into account when performing the NPV analysis. A pay back period of ten years was used for any loans taken for expanding facilities. The interest for the loans was based on the loan interest rates of the Bank of England and was set at 7%.

Table 4.12 Steps for calculating the portfolio NPV for each year of operation

Category	Year (t)				
	0	**1**	**2**	**...**	**n**
A. Total capital investment					
B. Revenue					
C. Running costs (without depreciation)					
D. Profit (B-C)					
E. Depreciation					
F. Taxable profit (D-E)					
G. Tax (33% of F)					
H. Net cash flow (-A+B-C-G+E)					
I. Discount factor $(\frac{1}{(1+r)^t})$					
J. Annual present value (H*I)					
K. Net present value $(\sum_{t=0}^{n} J_t)$					

4.5 CONCLUSIONS

This chapter has provided an overall discussion of the of the tool operation. The main uses of the tool and the way in which it can be used to assist in decision-making have been highlighted. Flow diagrams have been used to demonstrate the typical decision points that can be simulated in the process of drug development. Inputs into the model and the outputs from the tool have been summarised to provide an understanding of the capabilities of the tool. Much work has been put into collecting data that can be used as default data for the simulations. These have been presented along with other assumptions made.

The company-and drug-specific business and process characteristics all have been captured successfully and the resulting model is able to compute the time-to-market, cost, revenue and the risk, which all feature in the decision-making process. Simulating a portfolio of drugs and their development activities provide the management with the capacity to explore, in-silico, different strategies and to use the

insight gained to make real-life decisions that would add value in both short and long term to the new product portfolio of the company. The application of the tool is demonstrated through two case studies in the next two chapters.

CHAPTER 5

APPLICATION OF THE TOOL TO EXPLORE ALTERNATIVE DEVELOPMENT STRATEGIES

5.1 INTRODUCTION

Drug development under uncertainty is a challenging task for any biopharmaceutical company. The development work and the manufacture of material for clinical trials have to be planned so as to maximise the use of finite resources and capacity and to avoid delays in time to market. This would help to get the drug(s) first into the market and maximise the returns on investment. The aim of this thesis section is to demonstrate the tool's application during planning can help in deciding the development strategy for a portfolio of drugs. This tool can be utilised to help planning the allocation of resources and explore alternative strategies for executing the development work. The uncertainty and risk of failure is taken into consideration when applying the tool to aid decision-making. Several case studies will be used to illustrate the above applications.

Initially, in section 5.2 a brief description into the type of decisions that are made during drug development under uncertainty is presented, along with some examples from industry about the implications of these decisions. In Section 5.3 the background to the case studies is described which addresses the development of three monoclonal antibodies (MABs). In Section 5.4 a deterministic analysis of the problem is presented. The uncertainties in the problem are then identified using a sensitivity scouting analysis in Section 5.5. To demonstrate the decision-making objective of the model, a set of scenario analyses is carried out in Section 5.6. Finally in Section 5.7, Monte Carlo simulations are then used to imitate the randomness inherent in drug development. The case study involves deciding the best strategy for a small to medium size company considering whether to risk building a facility for

the commercial manufacture of the antibodies and if so, when, or whether to rely on a contract manufacturer for material for the clinical trials as well as for the market.

5.2 PLANNING AND MANAGING BIOPHARMACEUTICAL DRUG DEVELOPMENT

During the early stages of drug development, there is much uncertainty regarding almost every aspect of the development process. Strategic planning and efficient execution of drug development programmes are both desirable and necessary given the realities, economics, and regulatory requirements for approval of a drug or a biologic compound (Bernstein and Hamrell, 2000). Belated analyses of projects, which have been initiated without rational planning, could end up costs significantly exceeding anticipated revenues (Fisher and Pascucci, 1996). In the initial assessment of a new drug candidate, a series of estimates are made by experts in each field to predict its value to the portfolio (Johnson, 1998; Stonebraker, 2002). These range from predictions in dose levels to patient population captured by the drug and would also include estimations on cost and time scales. These forecasts are subject to uncertainty. Being better prepared to address these uncertainties will allow the company to deal with the risk that is present within a portfolio of new drug candidates.

The uncertainties could be technical or market related. Examples of technical uncertainty include dose levels and process efficiency. Market uncertainties relate to drug pricing and patient population share captured by the drug if and when it is launched. Given the varying resource requirements during the entire development process, it is vital to know in advance how much of these resources are required and when the need would arise. This would help to contain the cost of drug development, decrease time to market and minimise the negative impact of drug candidate failure.

Companies look to increase the value of portfolios in two ways (Keelin and Shew, 2003). In the short term, the investor confidence has to be boosted, while in the long term the expected net present value of the product portfolio has to be increased. By having a fixed and clear strategy for the management of the portfolio, the stakeholder's value is increased in the short term. Decisions regarding future work have to be geared to increase the portfolio NPV.

There are numerous methods for taking uncertainty into consideration. Sensitivity analysis is often used to determine the behaviour of performance measure to $\pm x$ % changes in each uncertain factor and hence determine the stability of the base case. For more sophisticated problems, where it is possible to assign probability functions for uncertain factors, the Monte Carlo simulation technique is a practical way of determining the impact of project uncertainties. Monte Carlo simulation is an analytical technique in which a large number of simulations are run using random quantities for uncertain variables and looking at the distribution of results to infer which values are most likely.

Scenario analysis is a process of analysing possible future events by considering alternative possible outcomes (scenarios). The analysis is designed to allow improved decision-making by allowing more complete consideration of outcomes and their implications. For example, scenario analysis can be used as a tool for manufacturing capacity planning for fluctuations in dose levels. Two way sensitivity analysis using contour plots is used in this chapter for the scenario analysis.

The final part of the section of the case study in this chapter revolves around the decision whether to invest in a facility or not and if doing so, when it is best to make that investment. Having a robust manufacturing strategy will contribute to the company's competitiveness (Demeter, 2003). Once a drug receives approval to be launched in the market, it is of vital importance to have sufficient manufacturing capacity to cater to the demand of the patient population. Not having this capacity would result in the loss of revenue. The best of example of this is Enbrel (rheumatoid arthritis, Amgen and Wyeth, USA), where the projected revenues for 2001 were in excess of US$ 1 billion (Grimster, 2003). However as the material was in short supply due to delays in the availability of the Rhode Island plant, the sales were only around US$ 750 million. This delay of material also resulted in the competitor product Remicade (Centocor, USA) gaining market share. The set up of the case study is presented next.

5.3 CASE STUDY BACKGROUND

A hypothetical case study that examines the use of the tool to plan and manage the development of a biopharmaceutical drug portfolio is presented next. The example is based on a company that has three potential products, all monoclonal antibodies (MABs), in its portfolio that are ready to go into clinical development. Although all three drugs are MABs, they are of different therapeutic classes with differences in the doses and the market sizes. This allows the portfolio to be diverse and makes the decisions relevant and challenging. The company was modelled as a small to medium size organisation, which had finite resources and defined manufacturing capacity.

Initially a deterministic case was set up and validated to ensure the outputs were calculated correctly. The cost, time to market and the portfolio NPV for a portfolio of three drugs were computed. Using these values as the base case, a sensitivity analysis was then carried out to determine the key parameters that affect the net present value (NPV) of a portfolio of biopharmaceutical drugs in development. Once this had been done, a series of scenario analyses were carried out to demonstrate the use of the tool to capture the effects of uncertainties in drug development. Finally, the tool was used to test out three different strategies for the manufacture of material for clinical trials and the market.

5.4 INITIAL DETERMINISTIC ANALYSIS

This section describes the key features of the process of drug development. The output data from the simulation of the portfolio of three drugs are discussed. These results give an understanding of the capabilities of the tool in simulating alternative strategies during the process of clinical development of drug candidates.

5.4.1 Setting up the deterministic case

The software tool developed in Chapter 3 was used to model the process of developing three drug candidates from the start of Phase I to the market. As described in Chapter 3, each phase of development was broken down into the following activities: development, manufacture of material for clinical trials and the clinical trials. In addition, the performance of an approved drug in the market was

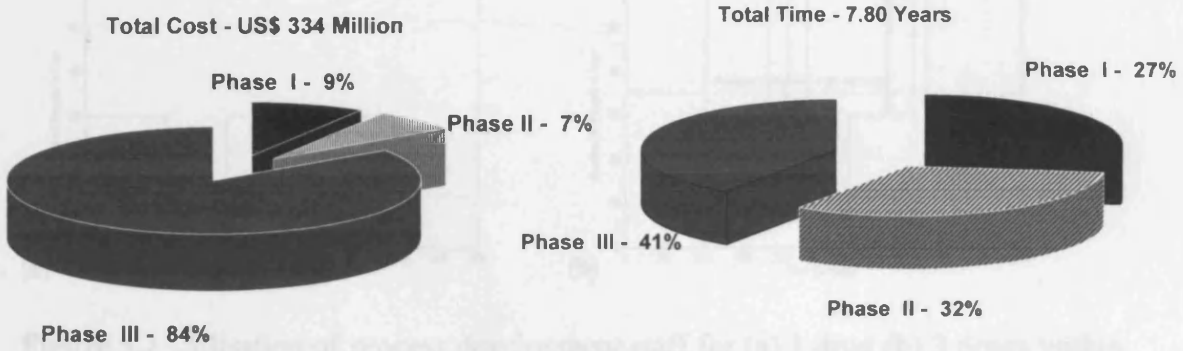
simulated for the remainder of its patent life. The input data presented in Chapter 4 was used for this case study. Only the first three drugs were used in the portfolio.

5.4.2 Deterministic results and discussion

5.4.2.1 Cost and time to market of drug development

Several simulations of drug development were carried out and the results are presented in this section. The cost and time to market are key factors in decision making in the process of drug development. The first set of results was generated to calculate the cost of the portfolio and the time to market for the three drugs in it for a set level of resources. The chance of failure and the uncertainties were not considered in the deterministic run. This was in order to establish the costs and time lengths involved in developing this set of drug candidates.

Out of the portfolio of three drugs simulated, the costs and time for a single drug are presented in Figure 5.1. The total cost to develop one drug was calculated by the model to be US$ 334.4 million (2002 US$). DiMasi *et al.* (2003) concluded in a detailed study that the cost of producing a drug to be US$ 404 million (2000 US$). However DiMasi *et al.* (2003) used mainly chemical entities for his study and the value presented is an average value. Therefore a direct comparison is not entirely correct. Also, the value calculated by the tool is for a specific drug and not an average value. Figure 5.1b shows the time taken for the development process. The longest phase is the third phase as it has the longest clinical trials involving over 2000 patients. Reichert, 2000, calculated the average time to market value for a MAB developed during 1991 to 1999 to be 7 years (82 months). The value calculated by the tool, 7.8 years compares favourably with this value. The cost and time values depend on the type of drug and the therapeutic area (Reichert, 2000).



(a) (b)

Figure 5.1 Breakdown of the cost (5.1a) and time length (5.1b) of development of one drug. The Phase III is the costliest and the longest as it has the largest clinical trials, which involve several thousand patients to prove the efficacy and long-term safety of the new drug.

5.4.2.2 Resource usage

A common problem encountered by companies is how to deploy staff to ensure projects are completed on time. Figures 5.2a and 5.2b show how the overall demand on personnel increases with the size of the portfolio but also indicate points of low activity and high demands. Being able to predict bottlenecks and poor use of human resources on the basis of simulation results allows companies to plan ahead and to anticipate how business decisions will impact at this level. For example, when only one drug is in development there are periods (e.g. weeks 100 to 180) where the process development staff are not being used. The average utilisation for this simulation is 12 personnel per week. However when three drugs are being developed, the average utilisation increases to 36 personnel per week and during the weeks 0 to 100 the process development personnel usage is at its peak value. In this case, the peak demands on the process development staff act as a bottleneck as only two drugs can be developed at any time. Thus the management could take steps to either increase the personnel or reschedule the development work.

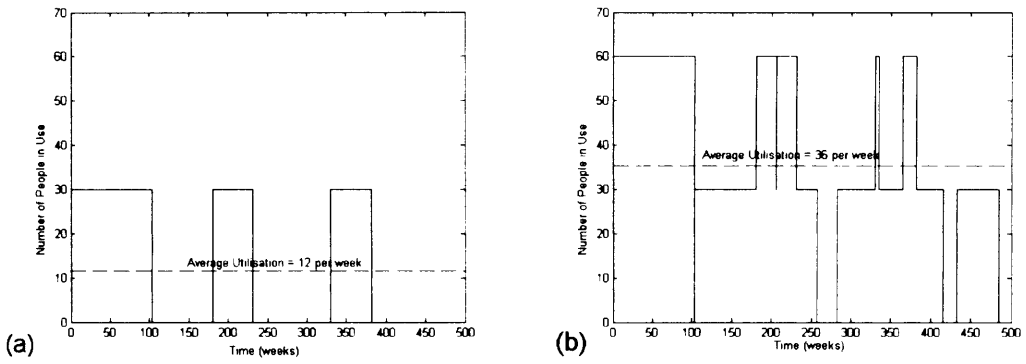


Figure 5.2 Utilisation of process development staff for (a) 1 drug (b) 3 drugs within the portfolio. When a higher number of drugs are in the portfolio, the durations where all the personnel are being used can be noted and used to avoid bottlenecks.

Raising capital for drug development is a challenging task due to the uncertainty in the cost and the probability of failure at any time. Therefore the ability to estimate as accurately as possible the demand on capital in advance will aid in making better decisions. Figure 5.3 shows the anticipated capital flow over the first ten years of development for the portfolio. It provides the management the level of investment needed and the time the demands will occur. The spend profile shows that there is a large demand on the capital between weeks 300 and 450. This is due to the fact that all three drugs enter Phase III trials during that time interval and the first drug is launched at around week 480. Phase III clinical trials are the costliest and launching a drug involves a high investment in an exhaustive sales and promotional effort (Stonebraker, 2002).

Having such a demand on the capital is not the ideal strategy and the company can make an effort to plan the development in order to have a less demanding spend profile, where very large investments are needed in a short duration of time. This could involve licensing out a drug or acquiring a strategic partner. This type of output would provide valuable insight to decision-makers in order to avoid delays due to shortage of capital.

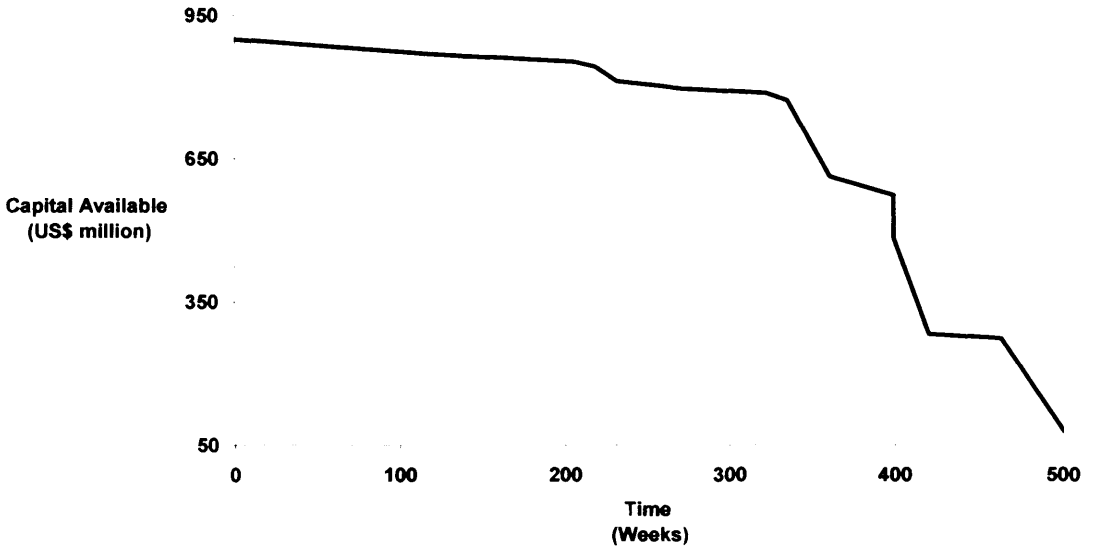


Figure 5.3 The predicted capital flow over the first ten years of the drug development process. Such data allows the management to anticipate the likely demand on capital and to plan ahead on fund raising.

5.5 IDENTIFICATION OF KEY UNCERTAINTIES

Although certain valuable conclusions can be made from a deterministic analysis, one cannot answer such questions as the likelihood of getting a particular drug to the market or of recovering the investments made during the development stages. Using a range of values, with their likely probabilities to estimate the future possibilities, rather than relying upon single-point forecasts, enhances the credibility of the analysis. Stochastic modelling with the Monte Carlo simulation technique was used to capture the degree of variability in the key influencing factors. Therefore to incorporate risk into the analysis, it was necessary at the outset to identify the variables that have the highest impact on the net present value (NPV) of the portfolio.

Each input was varied in turn while keeping the others constant. The % changes for each input are shown in Table 5.1 and were decided through literature (Stonebraker, 2002) and by consulting industrial experts (personal communication Rebecca Paulraj, Steve Froud, Lonza Biologics, Slough, UK; Brendon Fish, Cambridge Antibody Technology, Cambridge, UK). The % change in NPV relative to the base case value was plotted on a Tornado diagram (Figure 5.4). This form of analysis will

also aid in decision-making when allocating resources and planning the process of drug development.

Table 5.1 Percentage changes made to the different parameters from the base case values

Input	**Change to base case (%)**
Market share	± 50
Drug price set	± 20
Time spent in process development	± 50
Clinical trial time	± 50
Personnel available for process development	± 50
Presence of a competitor	+ 25
Mass per batch (In-House Production)	± 50
Market manufacturing cost	± 30
Product demand (Production Outsourced)	+100/-50
Contract manufacturing time	± 50
Product demand (In-House Production)	+100/-50

The sensitivity analysis results depicted in Figure 5.4 indicate that the critical driver of the portfolio NPV is the size of the market captured. This is then followed by the price set for the drug. The results are in agreement with those by Stonebraker (2002) who assessed the value of a new drug candidate and concluded that the NPV was most sensitive to the peak product share and the price per treatment. As the time to market is directly influenced by the time the drugs spends in process development and clinical trials, these two become the next most sensitive factors in drug development. The faster the drug gets into the market, the more time it has to generate revenue before a competitor or a generic drug is introduced.

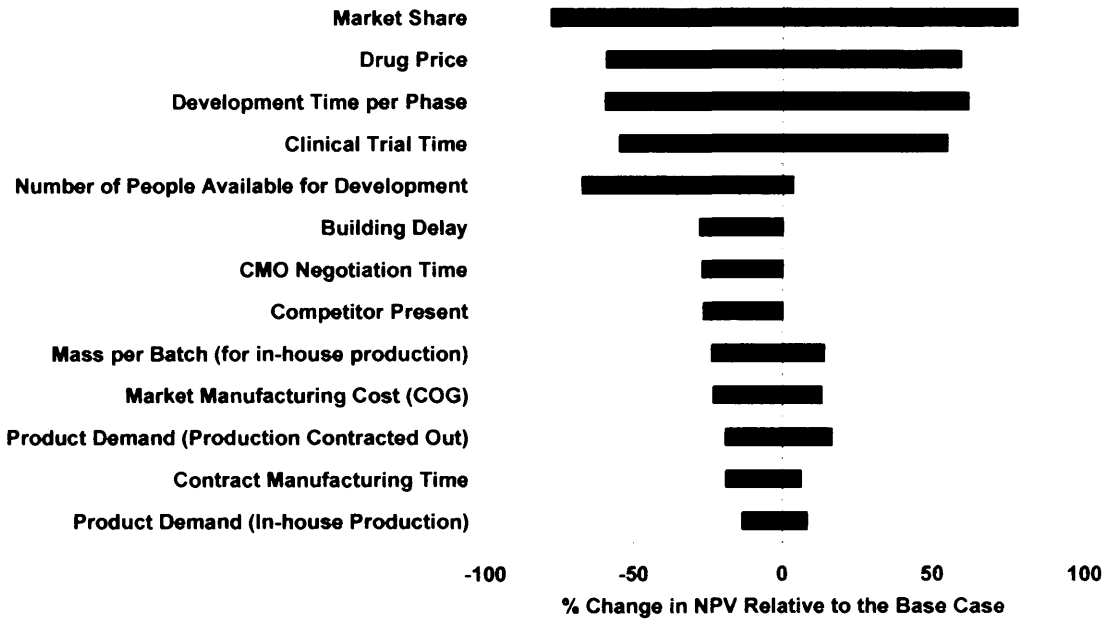


Figure 5.4 Tornado diagram showing the sensitivity of the portfolio NPV to input parameters. The vertical axis intersects the horizontal axis at the base case value. The market share has the biggest impact on the portfolio NPV followed by the drug price.

The number of personnel available for development work acts as a constraint, holding back the drug until the number of personnel required is available for the development work to be done. Therefore the number of people affects the time to market value directly and is a key driver of the portfolio NPV. The number of personnel needed for manufacturing and clinical trials were not modelled as constraining factors, and therefore they do not appear in the Tornado diagram. The manufacturing tasks were modelled with the availability of the facility as a constraint and the clinical trials were always outsourced to a contract research organisation, as is frequently the case in industry today.

Delays in building new facilities, delays in the negotiation time and the presence of a competitor all have a negative effect on the NPV. Dose levels (product demand) and the yields do not appear to be a major factor influencing the NPV of the portfolio. Therefore small increases in the quantities that need to be produced do not affect the NPV. The relatively low cost and duration of manufacturing tasks compared to development work and clinical trials can be cited as a possible reason for this. The probabilities of failure due to technical reasons and at clinical trials are influential factors, but have not been included as their effects are more intuitive. Therefore all

these results were generated assuming there were no failures due to technical reasons or at clinical trials.

5.6 SCENARIO ANALYSIS

Following the sensitivity analysis, a series of simulations were performed to illustrate the application of the tool to perform scenario analysis. In each of these, two parameters were changed simultaneously so as to study the effect of a combination of inputs on the portfolio NPV. The next sections describe the areas of drug development explored in each scenario analysis and the impact on the value of the portfolio. Again, the percentage changes to the two inputs were decided by consulting industrial experts (personal communication, Rebecca Paulraj, Steve Froud, Lonza Biologics, Slough, UK; Brendon Fish, Cambridge Antibody Technology, Cambridge, UK; Phil Morton, Delta Biotechnology, Nottingham, UK).

5.6.1 Scenario analysis set up

5.6.1.1 Process efficiency vs. time spent in process development

Early planning of process development activities and the appropriate allocation of resources to each stage of a product's clinical development can contribute substantially to the success of a new biopharmaceutical product and add value to the company (Byrom, 2000). One of the most challenging decisions that confront management is when to stop process development work and move forward into manufacturing for clinical trials.

The first scenario considered the time spent in process and product development and the improvements in yields achieved. The negative effects of process development delays can only be felt later if and when the drug gets into the market and fails to recover the money invested. The impact of varying the time spent in development (-75% to 50%) and the associated yields achieved (-75% to 50%), on the NPV was recorded. The results were plotted on a two-dimensional surface diagram to show how time in development and yields need to be balanced if an improved NPV is to be achieved.

5.6.1.2 Product demand vs. manufacture time

The analysis was extended to include uncertainty in the estimated dose levels and the manufacturing time of product for clinical trials. The dose levels required would initially be estimated by clinicians and confirmed towards the end of Phase II clinical trials or even as late as Phase III trials. Therefore manufacturing activities have to be planned according to the estimated dose levels and patient numbers needed for clinical trials. The product demand also encompasses non-clinical uses such as quality control and stability samples.

Having the capacity to predict the effect of fluctuations in product demand throughout development provides valuable data for planning. Such a scenario also relates to the occurrence of manufacturing delays, which can take place for a variety of reasons, from facilities not being available to batch failure occurring. On a positive note, adoption of different production routes could result in shorter production cycles and increased manufacturing output. A series of simulations were carried out in which the product demand (-50% to 150%) and the manufacturing times (-25% to 75%) were varied, while keeping all other inputs constant. The effect of these changes on the NPV was recorded.

5.6.1.3 Drug pricing vs. market share

The drug price and the patient population captured are each crucial to achieving high revenues/profits and for the recovery of investments. Government regulations and restrictions limit a company's ability to set the price for a new drug (Nicholson and Latham, 1994) and the presence of competitors means that a company needs a strong marketing strategy so as to capture a significant patient population and in order to make profits. Launching a new drug into the marketplace with the goal of achieving maximum penetration and exposure is an expensive advertising and public relations effort (Stonebraker, 2002). Therefore in the next scenario analysis, the drug price (±40%) and the market share (-75% to 25%) were varied to record the change in the portfolio NPV.

5.6.2 Scenario analysis results

The results of the different scenario analyses detailed earlier are presented in contour plots, Figures 5.5 – 5.7, which explore key decisions in biopharmaceutical drug development.

5.6.2.1 Process efficiency vs. time spent in process development

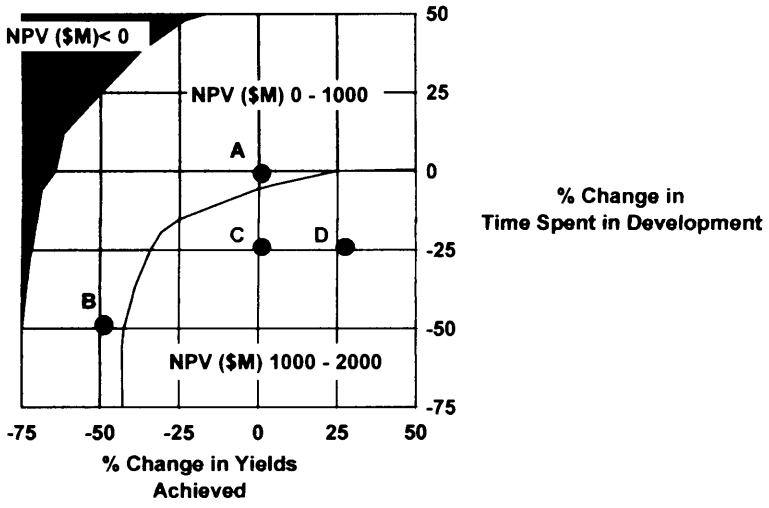


Figure 5.5 Portfolio NPV for variations in process development time and yields achieved. Points A, B, C and D refer to different options the management could deploy in planning process development work, with point A being the base case scenario.

Figure 5.5 illustrates the impact of variations in process development time and yields on the portfolio NPV. The point A marks the base case result. If the desired yields are not achieved by the anticipated deadlines or take longer to achieve, operation moves to the top left hand region of the figure and the NPV will eventually take negative values. Point B achieves the same NPV as A, but requires a less efficient process and hence less time spent in development. The resources saved by moving to point B can be applied to a different project. By moving to point C or D, the NPV will increase. In this case, the trade-off is between spending less time in development, resulting in either no efficiency gain (C) or an improved process (D). Point D gives the greatest improvement in NPV of the options considered.

This level of insight into resource usage is not obvious at first, but very much an asset to decision-making when allocating resources and planning for development programs. The process development group can use this type of output from the tool to keep a check on the yields and the deadlines necessary to achieve them. If the management feels that the process development team is falling behind, they can take steps to allocate extra resources in order to keep to the schedules or implement other actions to redress the situation. This type of study can be used to quantify the value of spending time in improving process efficiency and trade this against any resulting reduction in the time to market for the drug.

5.6.2.2 Manufacturing time vs. Product demand

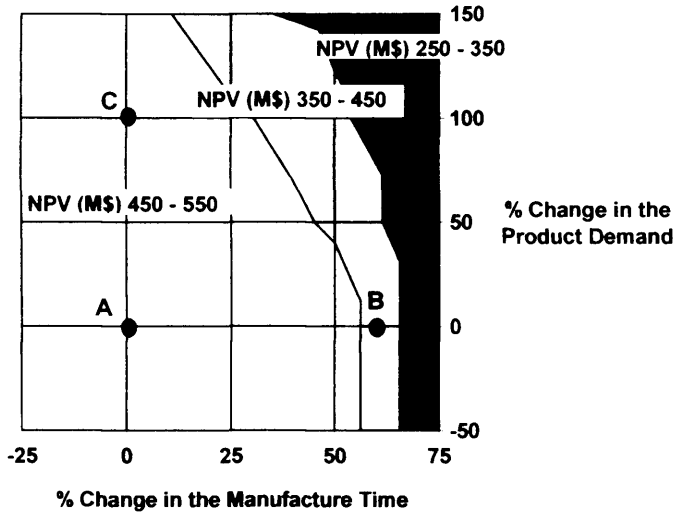


Figure 5.6 Portfolio NPV for the variation in the quantity of material and manufacturing time. Changes in the product demand and the manufacturing time do not seem to bring about a wide change in the portfolio NPV. Point A refers to the base case scenario.

The NPV of the portfolio is not highly sensitive to the manufacturing time and the quantity of material as shown earlier in the Tornado diagram (Figure 5.4). Changes in NPV to variations in both the quantity of material that has to be produced as well as changes in manufacturing times are plotted in Figure 5.6. If the manufacturing time increases beyond 50% of the base case value (2 months campaign time), the portfolio NPV becomes quite sensitive to the manufacturing time and drops of up to

US$100 million can be observed (point B). However an increase in the product demands does not influence the portfolio NPV as much as an increase in the manufacturing time (point C).

The above results would enable the management to feel confident about pursuing development work on a new drug candidate, which might have high uncertainty in the dose levels and plan for additional manufacturing capacity if required.

5.6.2.3 Drug pricing vs. market share

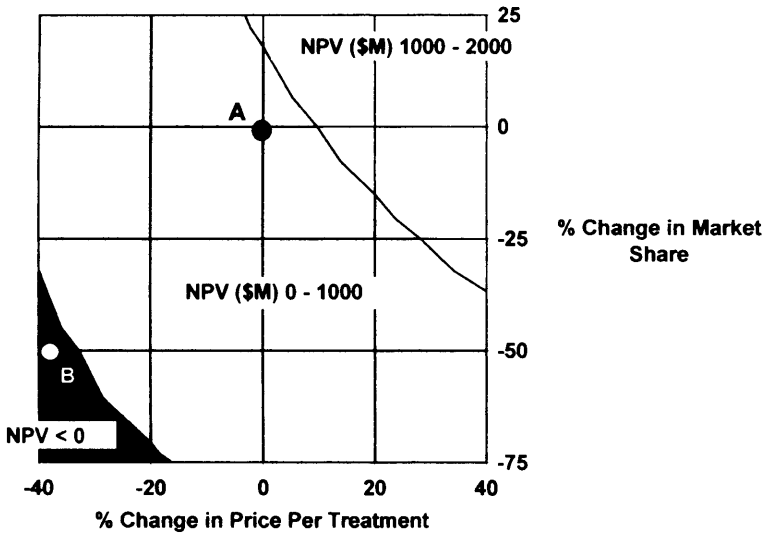


Figure 5.7 Portfolio NPV for the variation of the patient population and the price per treatment of the drug candidate. Point A refers to the base case scenario.

The results of changing the price of the drug and the market share on the portfolio NPV are shown in Figure 5.7. As the process of drug development is driven by the profits achieved in the market, it is important to gauge the effects of such fluctuations. The portfolio consisted of a set of breakthrough drugs (A). Lower market capture and an inability to command a high price could shift the portfolio NPV to point B, resulting in a negative NPV. The above results could be used to plan the sales strategy and make judgement on which markets to launch the drug. If the company feels that there is too much competition or the drug is too expensive to get

approval from the authorities, using this type of scenario analysis the project could be terminated at an early stage or be held back.

5.7 IN-HOUSE VS. CONTRACT MANUFACTURING

The sensitivity analysis was used to identify the key uncertainties in Section 5.4. The major technical and market uncertainties were incorporated into the final case study presented in this chapter. This case illustrates the application of the tool to aid in decision-making in biopharmaceutical development under uncertainty. The outputs are depicted and an illustration of how such results from Monte Carlo simulations can be interpreted is provided.

5.7.1 Case study background

This example was based on a biopharmaceutical company with a pipeline of three monoclonal antibody candidates. The company is considering whether to risk building a facility for the commercial manufacture of the antibodies and if so, when to sanction construction, or whether to rely on a contract manufacturer throughout. The use of contract manufacturing organisations (CMOs) for the delivery of material can range from just process development work to the full manufacture of material and is a key feature of the biopharmaceutical industry (Byrom, 2000). The options in terms of outsourcing manufacture or building capacity for in-house manufacture must be weighed carefully and will in all events be constrained by the resources available.

The decision to build a cGMP facility takes considerable time and cost and risks having a facility lying idle if products fail at clinical trials (Langer, 2004). Opting for a contract manufacturer offers potential time savings, which can be critical to a drug's market share and success. However, contract manufacturers are expensive and the company will have to relinquish control over the manufacture of material. The software tool was used to model and analyse the different options that were available for manufacturing of material for clinical trials and eventual sales.

The three options considered were:

1. Build Early Option (Aggressive)

   The facility is used for the production of material for the clinical trials and building a new plant starts when the first drug reaches the end of Phase II clinical trials. In this case the manufacturing plant will be ready to supply product(s) to the market upon approval. This is an aggressive and risky strategy.

2. Contract Manufacturing Option (Cautious)

   The production of material for the clinical trials and the market is outsourced to a CMO. No building work is required. This is a cautious strategy, but does mean the company has less control over manufacturing.

3. Build Late Option (Conservative)

   The material for the clinical trials is produced within the existing plant and a new facility is built once the first product successfully completes Phase III clinical trials. This would enable the company to start producing its first approved drug in-house by the third year into the market. While the facility for commercial production is being built a contract manufacturer is used for the first approved drug. It is a cautious strategy but one which results in more company control of manufacturing.

The three options were analysed in two different ways. The first was a deterministic approach where the uncertainty in the different parameters and the risk of failure of drugs were not taken into consideration. In the second approach, Monte Carlo simulations were used to capture the risk in each of the options. The aim of using these two approaches to analyse the three options was to highlight the impact of incorporating risk and uncertainty into the options. The following sections describe the data used for the case study and the probability distributions assigned to the key uncertainties.

5.7.2 Deterministic case set up

The input data presented in Chapter 4 were used for the deterministic study (Tables 4.1 to 4.10). It was assumed that whenever the manufacture of clinical trial material was outsourced, some of the research and development work was handled by the same contract manufacturing company. Drugs that completed the development work successfully then proceeded to the market where a set sales profile was applied.

5.7.3 Monte Carlo set up

Next the chance of failure and distribution probabilities to the key parameters was assigned in order to perform Monte Carlo simulations. The phase transition probabilities for the MABs were kept the same for all three options (Table 4.11). However the probability of failure due to technical reasons was assumed to change depending on the option selected (Table 5.2). When a CMO was involved the probability of a drug failing due to technical reasons was assumed to be low reflecting the fact that there is experience and knowledge available to the company from the CMO regarding process and product development (personal communication, Richard Francis, Protherics, UK).

Table 5.2 Probability of failure due to technical reasons

	Without a CMO	**With a CMO**
Probability of failure due to technical reasons	0.30	0.10

The key uncertainties identified in the sensitivity analysis study in Section 5.5 were assigned with probability distributions for this case study (Tables 5.3 and 5.4). These values were determined from literature sources and through discussions with industrial experts (personal communication, Rebecca Paulraj, Lonza Biologics, Slough, England).

Table 5.3 Parameters that were assigned with probability distributions

Build early option	**Contract manufacturing option**	**Build late option**
Building cost	Delays in contract	Building cost
Building completion time	negotiation	Building completion
Price per treatment	Delays in material	time
Patient population	delivery	Price per treatment
	Price per treatment	Patient population
	Patient population	

The facility, estimated at $200 million (Langer, 2004) was expected to be able to produce three monoclonal antibodies at 200 kg per year under cGMP condition and was expected to be completed in three years (personal communication, Steve Froud, Lonza Biologics, UK).

Table 5.4 Key parameters and their probability distributions

Parameter	**Possible values**	**Probability**
Negotiation time	3 months	50%
	6 months	30%
	12 months	20%
Delays in material delivery (CMO)	0 months	60%
	3 months	30%
	6 months	10%
Cost of facility	US$ 200 million	60%
	US$ 250 million	30%
	US$ 180 million	10%
Time for completion of facility	3 years	90%
	4 years	10%
Price per treatment	80% * Base case estimation	50%
	Base case estimation	30%
	120% * Base case estimation	20%
Market share	60%*Base case estimation	50%
	Base case estimation	30%
	110%*Base case estimation	20%

Making accurate predictions about market sizes for new products is notoriously difficult and estimating market share for a company's own product is hard as there are a large number of influencing factors such as pricing, sales efforts and competitive moves (Brastow and Rice, 2003). Therefore wide distributions from the

base case values were assigned to the price per treatment and the market share. The values and the probabilities assigned were decided upon much discussion with industrial experts (personal communication, Rebecca Paulraj, Steve Froud, Lonza Biologics, Slough, UK; Brendon Fish, Cambridge Antibody Technology, Cambridge, UK; Phil Morton, Delta Biotechnology, Nottingham, UK).

Once the major technical and commercial uncertainties were identified and incorporated into the analysis, it was possible to run Monte Carlo simulations to assess the impact on the portfolio NPV. The blocks that assign the probabilities to the parameters were activated within the tool for this purpose. Having validated the results of a single simulation in the deterministic analysis, 400 simulations were carried out for each option. At the end of each simulation, the inputs used and the outputs generated were saved. To determine the number of simulation runs required to reach convergence, running averages of the key output, the NPV were monitored until they levelled off. The next section discusses the results from the deterministic approach as well as the Monte Carlo simulations technique.

5.7.4 Results and discussion

5.7.4.1 Deterministic results

Figure 5.8 shows the results of the deterministic study that does not account for drug failures. The tool predicted that the option to build early, at the end of Phase II clinical trials, is the most attractive followed by the option to build after the product makes it to the market. The lower portfolio NPV associated with the build late option can be attributed to the high contract manufacturing costs in the first three years in the market and the high marketing costs involved in launching the product which combine to lower the profits made. However, the build late option is still marginally better than the contract manufacturing option (by 10%) due to the savings made by manufacturing in-house during development and once the commercial facility is built.

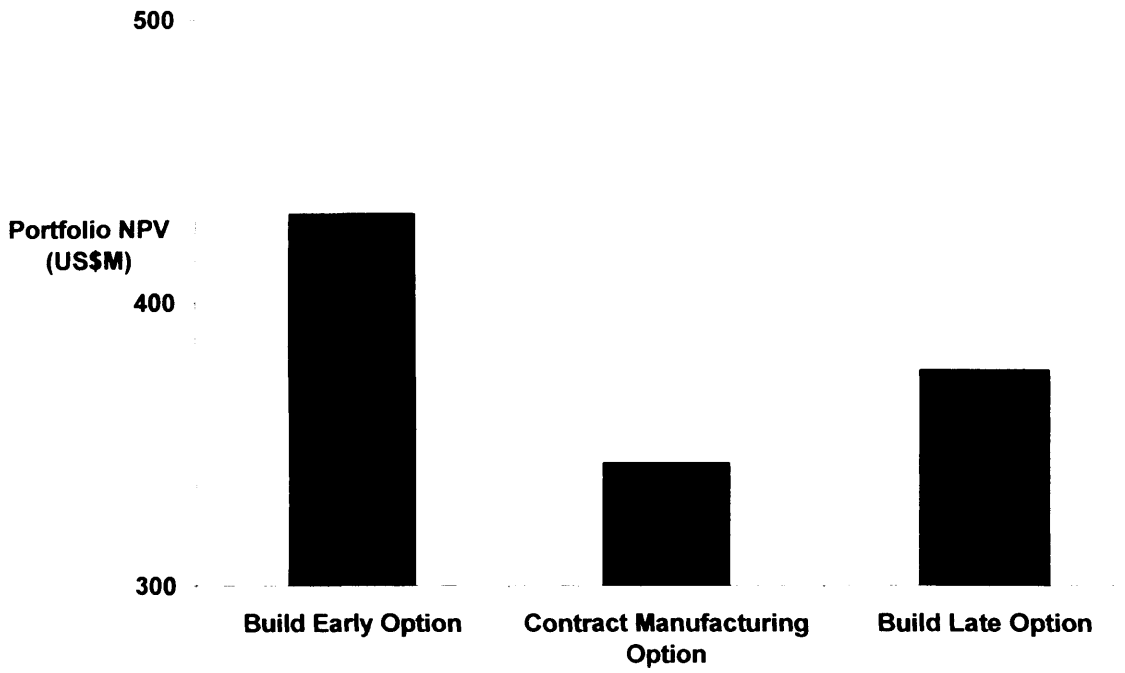


Figure 5.8 The portfolio NPV for the three options without the uncertainty and risk incorporated. The aggressive option of building early has the highest portfolio net present value.

5.7.4.2 Monte Carlo results

Figure 5.9 shows the distribution of the portfolio NPV for the build early option. The distribution is skewed to the left, as most of the NPV values are negative due to losses made when drugs fail to reach the market. Figure 5.10 shows the frequency distribution of the portfolio NPV for all three options. This indicates that there is a wide spread of possible portfolio net present values in each, as well as a high degree of overlap. Each of the graphs shows at least two peaks. The first corresponds to the conditions where drugs fail and the second is due to the financial rewards achieved when drugs succeed in making it to the market. Blau *et al.* (2000) also reported the occurrence of two peaks for the distribution of NPV values for a portfolio of drugs. Ideally the distribution with higher NPV values and with the least dispersion of NPV values would be the preferred option. However, this is not clear from the Figure 5.10 due to the multiple peaks and the overlap between the three options.

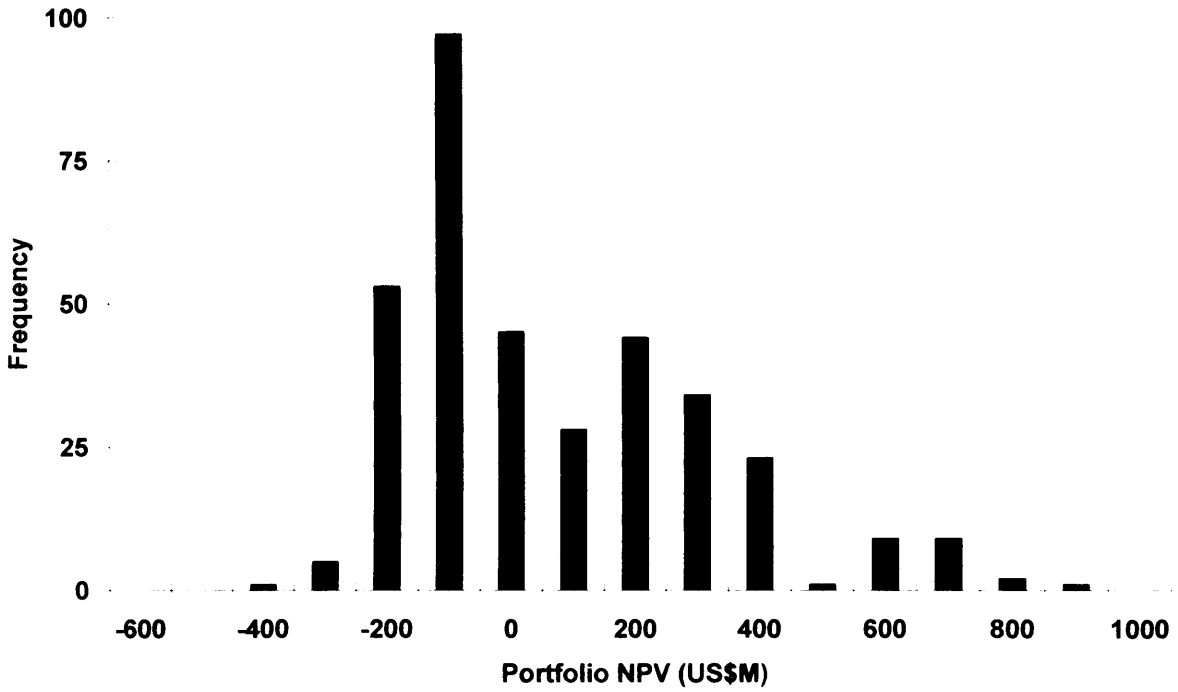


Figure 5.9 The NPV distribution from the Monte Carlo simulations for the build early option. Majority of the portfolios have a negative NPV due to the drug candidates failing during the clinical trials.

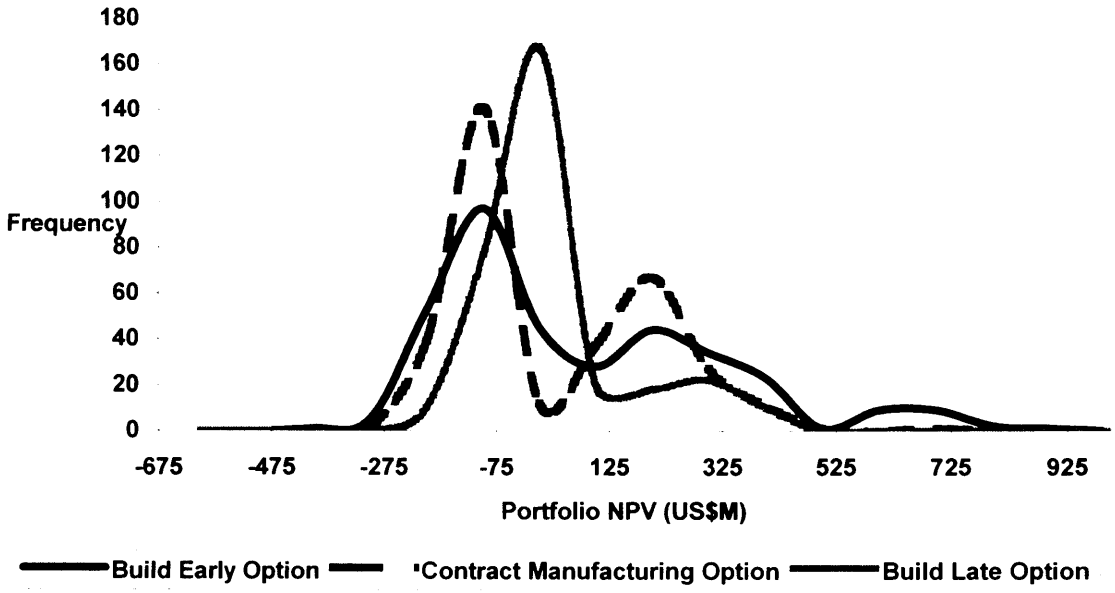


Figure 5.10 Frequency distribution of the expected portfolio NPV for the three options. The net present values for the three options show much overlap and each graph has at least two peaks.

From the frequency distributions in Figure 5.10, it is possible to calculate the mean (expected portfolio NPV) and standard deviation (risk) of each option and compare

them. The outputs generated by the Monte Carlo simulation technique are shown in Figure 5.11. Factoring in risk and the uncertainty reduces all the expected net present values (Figure 5.11) relative to the deterministic value (Figure 5.8) due to the fact that many drugs fail in clinical trials or for technical reasons. The option with the highest NPV and the lowest risk is preferred. The best option in terms of reward (expected NPV) is the build late option, which is building after at least one drug gets into market. However, the best option in terms of minimising risk is the contract manufacturing option.

Considering all three options, the expected NPV values are within ± US$ 20 million of each other and yet the risk values are between ± US$ 85 million and ± US$ 251 million. This high degree of overlap between the options results in the t-test showing no significant difference between them in terms of the expected NPV (Table 5.5). Therefore the decision is most likely to be based on the risk involved with each option. The option of using a contract manufacturer is the least risky as there are no high investments in new facilities to be recovered. Also the contribution from the CMO in terms of knowledge and experience serves to lower the risk of failure due to technical reasons. The risks in this option, for example delays in negotiation and material delivery, do not appear to have a major effect.

The option of using a contract manufacturer is a cautious strategy. However, if the management is willing to tolerate a higher risk in order to get a higher expected portfolio NPV, the best option would be the build late option. While the risk is minimised by setting the minimum requirement of at least one drug into the market before building, the revenue increases relative to the contract manufacturing option, as it has control over the manufacturing of material after the first three years. The risk is still high as the revenue from just one drug is insufficient to recover the full investment on the facility. If the success of two drugs is set as the minimum requirement for starting to build, the risk involved with the option of building after the product gets into the market will be much lower. This decision is further justified by the fact that even if only one drug makes it to the market from this portfolio, other new drug candidates, which might follow (and have not been considered in this case study) could be produced in the same facility.

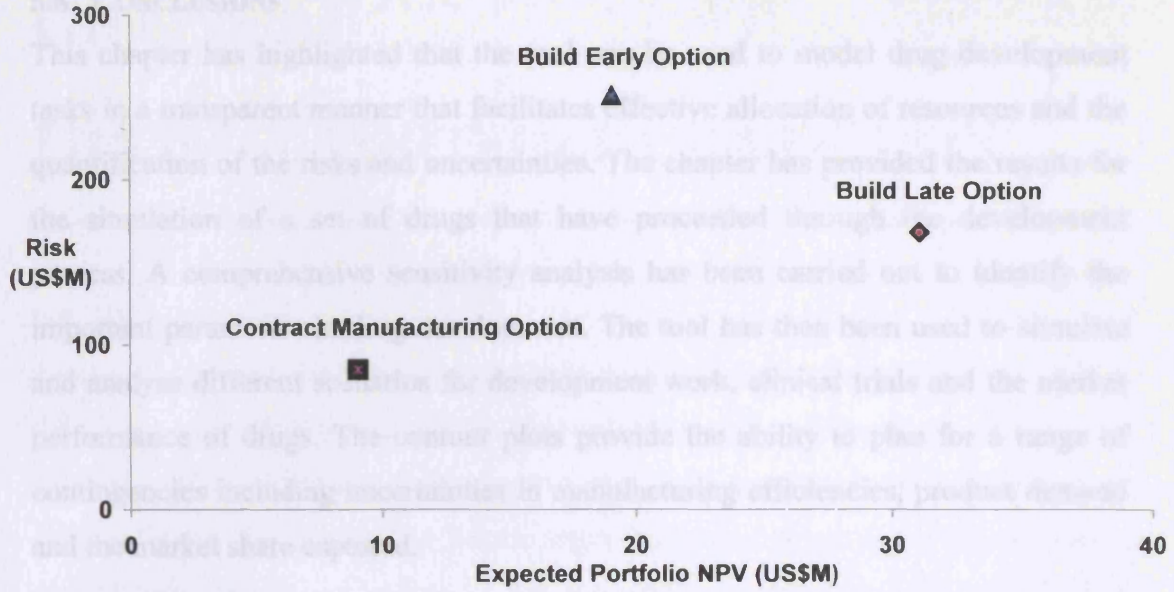


Figure 5.11 The reward and risk associated with the three options, after the uncertainty and the risk involved have been factored in. The build late option has the highest expected portfolio NPV, while the build early option has the highest risk.

Table 5.5 Expected values and standard deviations for the three options

Performance Measure	Statistic	Value		
		Build early	Contract Manufacturing	Build late
NPV	Mean	19	9	31
	Standard deviation	251	85	168
	t-statistic*	N/A	0.53	-0.76

*Indicates the statistical significance relative to the baseline build early option. An absolute value of greater than 1.645 is considered significant at the 5% level.

Accounting for failures and uncertainties knocks the build early option out of first place, highlighting the limitations of relying solely on deterministic results. The option of building early is the second best in terms of reward but has the highest risk. This is because in case none of the drugs making it to the market, the company is saddled with a high investment that cannot be recovered. However when two or all three drugs do make it to the market, the profits are substantial.

5.8 CONCLUSIONS

This chapter has highlighted that the tool can be used to model drug development tasks in a transparent manner that facilitates effective allocation of resources and the quantification of the risks and uncertainties. The chapter has provided the results for the simulation of a set of drugs that have proceeded through the development process. A comprehensive sensitivity analysis has been carried out to identify the important parameters in drug development. The tool has then been used to simulate and analyse different scenarios for development work, clinical trials and the market performance of drugs. The contour plots provide the ability to plan for a range of contingencies including uncertainties in manufacturing efficiencies, product demand and the market share captured.

A case study has been used to demonstrate the functionality of the tool to output the expected net present value (NPV) of a small drug portfolio under uncertainty for different manufacturing options. The effects of technical and market uncertainties on the question of whether to build or use a contract manufacture were analysed using Monte Carlo simulations. The simulation studies highlighted the benefits of incorporating uncertainties when ranking different strategies. Effective use of the simulation outcomes can lead to risk mitigation, more effective use of resources and improved overall economic performance. This provides an extra dimension to the decision-making process where decisions can be based on both the expected NPV and the likelihood reaching a critical NPV.

In this hypothetical case study, depending on the level of risk that the management is willing to tolerate, the decision would vary. A cautious strategy would be to contract out the manufacturing of materials. By contracting out the company can defer high investments in facilities. Whereas a management that would be risk taking would select the option of building a facility once a single product makes it to the market. The next chapter describes how the tool can be utilised to select the optimal portfolio under a given level of resources.

CHAPTER 6

OPTIMAL PORTFOLIO SELECTION

6.1 INTRODUCTION

One of the greatest challenges facing the biotech industry in the new century will be the process of selecting which new products to develop (Blau *et al.*, 2000). The product pipelines of pharmaceutical companies are in a constant state of flux as new drug leads are identified and products reach the market or are discontinued during development because of safety or efficacy concerns (Rogers *et al.*, 2002). The pharmaceutical companies are now under increasing market pressure from managed healthcare organisations, the entrance of branded competitor drugs and competition from expired-patent generic drugs (Rogers *et al.*, 2003). The process of drug development is complicated by the fact that each project is subject to technical and market uncertainties. In the pharmaceutical industry, a firm needs to consider its entire product portfolio in the context of market and technical uncertainty, budgetary constraints and the desire to balance the portfolio across many drug type classifications (Blau *et al.*, 2000; Sharpe and Keelin, 1998; Subramanian *et al.*, 2000). However, to date many R&D managers are not satisfied with the existing portfolio selection models (Cooper *et al.*, 1997). As a result, the optimal management of the new product pipeline has emerged at the foremost of all strategic planning issues within such companies (Rogers *et al.*, 2002).

Approaches to portfolio management differ, depending on whether the decision-making process revolves around the prioritisation of the portfolio products or around the company's strategic direction, which groups preferred products in terms of key properties (Soegaard, 2003). A review of all the product portfolio selection and management techniques was provided in Chapter 1. High quality decisions about determining long-term business strategy often require explicit analysis of uncertainty. Proponents of risk analysis argue that increased risk information improves management's understanding of the nature of risks, helps identify the major threats to project profitability and reduces forecasting errors (Ho and Pike,

1998). Understanding the array of possible outcomes and key sources of uncertainty provide management with a key tool to manage and balance the portfolio.

Effective portfolio analysis can identify the optimal portfolio in terms of value creation and its risk for any given set of constraints. The company's business strategy is then applied through the selection of products for development. The previous chapter illustrated the use of the tool developed in this PhD to model alternative development strategies and to perform scenario analysis. In this chapter the tool is applied to quantify the risk and reward of different drug candidate portfolios to aid decision-making in product portfolio selection. Incorporating the ability to perform risk analysis on the product portfolio enhances the capability of the tool and adds quality to the decisions made using it. A combination of two traditional methods is proposed as an effective mechanism to capture the reward and risk present in a portfolio of biopharmaceutical drug products. The use of the tool to apply the method is demonstrated through a hypothetical case study.

This chapter is structured as follows. Section 6.2 provides a description of the proposed method to assess the risk and reward of different drug portfolios. An overview of how this is applied using the tool is presented. A case study is presented in Section 6.3 to demonstrate the application of the method using the tool in computing the value and risk of different portfolios under resource constraints. The chapter ends with a set of conclusions about assessing the value and risk of different product portfolios.

6.2 METHOD DESCRIPTION

6.2.1 Introduction

An approach that combines two traditional methods is proposed as an effective mechanism to capture the risk and reward present in a portfolio of biopharmaceutical drug candidates. One way to make decisions about such a portfolio is to use the efficient frontier method derived by Harry Markowitz (1952, 1991). The portfolio theory was developed to select company shares and maintain an optimal share portfolio.

This theory is based on three major precepts:

1 A theoretical rational investor – Markowitz (1952, 1991) asserts that a rational investor is not indifferent to risk and will choose more value over less value, but will also prefer less risk to more risk;
2 There is more than one optimal portfolio – it is sometimes possible to find a better expected return by tolerating more risk, but this may not be always be acceptable;
3 The portfolio as a whole is more optimal than its individual projects – each project or investment must be considered in the context of what it contributes to the entire portfolio. For example an optimal portfolio of five investments does not always contain the five 'best' investments.

Based on this understanding, Markowitz (1952, 1991) defines a portfolio as being efficient if two conditions are met:

1 No other portfolio exists that has a greater expected return and a lower level of risk.
2 No other portfolio exists that has less risk and a higher expected return.

If one or both of these conditions are not true, a portfolio is said to be inefficient. When all portfolios are plotted on a graph of value vs. risk, the efficient portfolios appear on a line called the "efficient frontier". There are no viable portfolios above this line (Figure 6.1). Once all the efficient portfolios are plotted, the company can make informed decisions regarding their portfolio selection, balancing acceptable risk with the highest possible return.

It is possible to locate this efficient frontier line using the approach described by Markowitz (1952, 1991). However an alternative method, using Monte Carlo simulations, provides a more convenient way to capture the features and complexities found in the field of biopharmaceutical drug development. This particular method has been suggested by McVean (2004) as a suitable approach to assessing different portfolios in the petroleum industry. Walls (2004) demonstrated through a case study the application of the efficient frontier method in oil exploration and production. Rogers *et al.* (2003) demonstrated an efficient frontier for the selection of a drug portfolio for a pharmaceutical company. However, no

applications of the 'efficient frontier' approach could be fond in the literature in the field of biopharmaceutical portfolio selection. The Markowitz method is described next, followed by the application of the Monte Carlo method.

6.2.2 Markowitz approach

Markowitz outlines a mathematical technique for deriving the efficient frontier for selecting a portfolio of stocks (Markowitz, 1952; Markowitz, 1991). It should be noted that the description of the efficient frontier was originally formed around a discussion of securities investments, but it can, at least in principle, be applied to the biopharmaceutical product portfolio selection. As in many other analysis/optimisation techniques, the Markowitz method requires a high level of information to be collected for each project and for it to be converted into a format that could be used as there is in performing the actual analysis.

There are five steps that must be completed in order to determine the efficient frontier:

1. The expected value of each project under consideration is estimated.
2. The variance in the potential value (e.g. NPV) of each project is estimated as a measurement of risk.
3. The correlation between each project and every other project is estimated.
4. The constraints that limit which portfolios are acceptable are expressed in the form of simple linear equations.
5. Once all of this information has been collected, an analytical expression for the efficient frontier is determined.

A detailed description of this method is not appropriate for this discussion, however, the end result, after considerable linear algebra and matrix manipulation, is the efficient frontier line on a value vs. risk graph (Figure 6.1). Any point on this line has a corresponding equation that represents a portfolio of projects. Moving up the efficient frontier line, results in an increase in both value and risk (Figure 6.1).

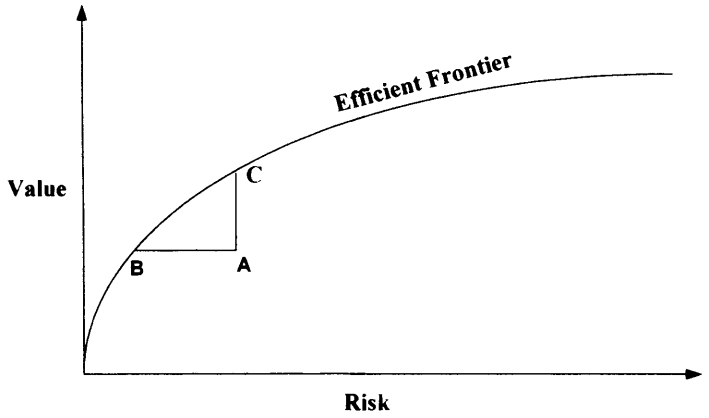


Figure 6.1 The efficient frontier is a line that connects all the efficient portfolios. The portfolio at point A is less efficient to a portfolio at B, as it has more risk for the same value. The portfolio at point C provides more value for the same level of risk and is hence superior to all of the other solutions at A and B.

In order to perform Markowitz' efficient frontier analysis, some key information must first be assembled, e.g. the expected NPV and the risk of each project. The manner in which this information is compiled is not always straightforward. Historical data, if available, can provide some indication to future performance. Comparison with similar projects may also yield appropriate information. Industry experts might be able to provide expert knowledge but by definition this is likely to be more subjective. By contrast the Monte Carlo method relies less on opinion. Of all the information required, the correlation between a project's performance and that of other projects may be the most difficult to ascertain. The next section describes how the application of Monte Carlo simulations can be used to generate the efficient frontier of portfolios.

6.2.3 Monte Carlo method

Monte Carlo simulation is an analytical technique in which a large number of simulations are run using random values for uncertain variables. This yields a frequency distribution for each of the output parameters, from which the expected value and risk (standard deviation) can be calculated. In order to perform Monte Carlo simulations, it is first necessary to identify key uncertain inputs parameters using a sensitivity analysis. Then probability distributions must be applied to these key uncertainties. Subsequently, an appreciable number of Monte Carlo simulations

must be performed to generate the expected value and risk for the individual projects (Figure 6.2).

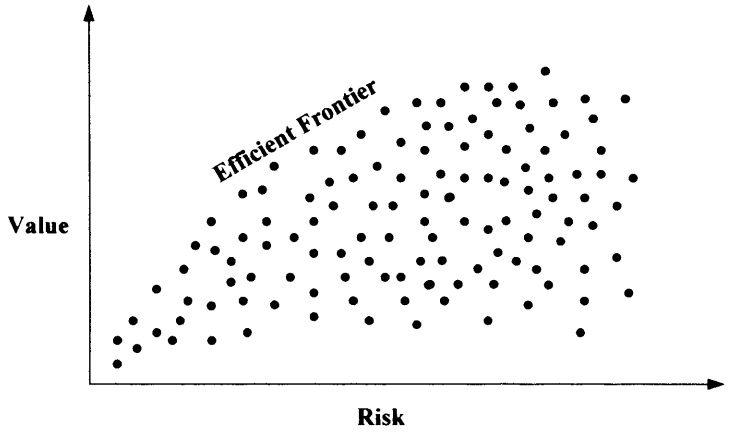


Figure 6.2 Using Monte Carlo simulations create a random collection of possible portfolios. The upper boundary created by the portfolio will form the 'efficient frontier'.

6.2.4 Comparison of the methods

The traditional Markowitz approach uses variance as a measure of risk for the individual investment opportunities. The implicit assumption is that the risk profile for an opportunity is fully specified by its mean and variance. Essentially, all risk profiles are approximated by a normal distribution. In drug development, this is not always the most appropriate type of approximation. For example, the sales and drug pricing can have a skewed distribution and projects can be abandoned at any stage of development.

In the Monte Carlo method different types of distributions can be assigned to the parameters (Figure 6.3). For example, the probability distribution used to describe the price set for the drug will be different to that of the development cost. Different types of distributions (e.g. triangular, normal etc...) can be applied in order to capture the risk profile that describes the biopharmaceutical drug development process best. Literature and the opinion of industry experts can be used to identify the most appropriate distribution for each parameter. Stonebraker (2002) presents a method where the opinion of experts is used to help assigning distributions for the key parameters in drug development.

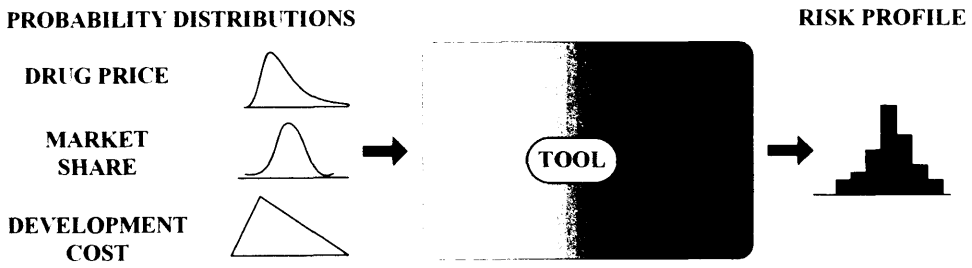


Figure 6.3 Different probability distributions can be assigned to the significant uncertain variables. Monte Carlo simulations are then carried out until a confident risk profile is generated.

As part of the efficient frontier analysis, the correlation between the projects within a portfolio has to be established. As the projects are resourced from the same resource pools (both, renewable and non-renewable) the interaction between the projects will be captured. Having established the basics of the model, the application of the method utilising the tool is illustrated through a hypothetical case study.

6.3 CASE STUDY

6.3.1 Background

A hypothetical case study that computes the reward and risk in different portfolios of drug candidates will now be presented. The reward is measured as the expected NPV and the risk is taken as the standard deviation of the NPV distribution. The study is based on a company with six potential monoclonal antibodies that are ready for clinical development (Table 6.1). Given the finite level of resources available, the company is unable to take all six into clinical development. The objective of the case study is to provide decision-makers with an explicit view of the rewards and risks of different portfolios in order to decide which drugs the portfolio should consist of. These results are presented to demonstrate the type of analysis that can be carried out using the prototype tool.

The drug portfolio of six drug candidates presented in Chapter 4 was used for this case study. The drug characteristics are summarised in Table 6.1. In order to make the portfolio selection decisions more realistic and challenging, the set of drugs used was selected to contain characteristics that are quite different in all possible aspects

of drug development (e.g. market, price, therapeutic area etc.). Next, differing levels of uncertainty were assigned to further diversify the potential products (Table 6.2). The drug portfolio selection problem was then carried out under three different resource levels as constraints in order to illustrate the range of options available to decision makers.

Table 6.1 Description of the drugs in the portfolio

Drug candidate	Market share*	MAB type	Comments
A	High	Chimeric	New drug
B	Low	Humanised	New indication
C	Medium	Chimeric	New drug
D	Very high	Chimeric	Blockbuster
E	Low	Murine	New drug
F	Low	Chimeric	New drug

*Market share = dose x price x patient population

Table 6.2 Level of uncertainty assigned to each drug candidate

Drug candidate	Uncertainty
A	Medium
B	Very low
C	Medium
D	High
E	Medium
F	Low

The next section describes the steps carried out to generate the efficient frontier for portfolio selection at different resource levels using Monte Carlo simulations.

6.3.1 Sensitivity analysis

The sensitivity analysis carried out in Chapter 5, (Figure 5.4) was used to identify the top seven inputs that impact on the portfolio NPV:

- Market share of drug
- Drug price per patient
- Development time
- Clinical trial time
- Mass per batch
- Delays in material delivery
- Manufacturing cost (COG)

Although the number of personnel for process development work was shown to be a significant factor in Figure 5.4, it is a company specific attribute and has been used as a resource constraint in this case study. The building delay and CMO negotiation time delay parameters result in a delay in manufacturing material for clinical trials and the market. Therefore both of these were included together as a simple factor 'Delays in material delivery'. By varying the market share, the effects of a competitor being present were accounted for.

6.3.2 Assigning distribution parameters

Probability distributions were assigned to the parameters that the portfolio NPV was most sensitive to (Table 6.3). The distributions were based on literature (Myers and Howe, 1997; Stonebraker, 2002) and discussions with experts from the industry (Rebecca Paulraj and Steve Froud, Lonza Biologics, Slough, UK; Brendan Fish, Cambridge Antibody Technology, Cambridge, UK). The probabilities were assigned to reflect the level of uncertainty attributable to the characteristics of the drugs in Table 6.2. For example, drug D was modelled as a project with high risk and reward was assigned a negatively skewed distribution for the development time to reflect the increased likelihood of delays. All the values used in this case study are presented in Appendix A.

Table 6.3 Key parameters and type of distribution assigned

Parameter	Probability distribution
Market share of drug Drug price per patient	Normal distribution, five discrete values
Development time Clinical trial time Product yield Delays in material delivery Manufacturing cost (COG)	Skewed distribution, three discrete values

The clinical trial failure rates on Table 4.11 were used for this case study. The chance of failure due to technical reasons was again set according to the uncertainty level assigned to the drug candidate with drugs with high risk having a higher chance of failure due to technical reasons (Table 6.4). As drug B was a new indication for an existing drug there was no technical uncertainty involved in that drug candidate.

Table 6.4 Probability of failure due to technical reasons

Drug candidate	Probability of failure due to technical reasons at PIII (%)
A	20
B	0
C	10
D	30
E	5
F	15

6.3.3 Setting up the Monte Carlo simulations

The first simulation was carried out with all six drugs in the portfolio and no resource constraints being applied. This was performed in order to compare to the results from the resource-constrained simulations. Next, three resource levels of US$ 500, 750 and 900 million were defined as constraints and simulations carried out for each to identify the number of drugs that could be supported in the portfolio at each of these levels (Table 6.5). The probability of failure for the drug candidate during development and all the other uncertainties were not applied during these

(deterministic) simulations. The highest number of drugs progressing into the market under each resource level was taken as the number of drugs per portfolio for the rest of the case study. For example, at resource level of US$ 500 million, three drugs made it to the market. Therefore the number of drugs supported at that level was set as three. As six drug candidates were taken into consideration, there were 20 possible combinations at this resource level (Table 6.5).

Table 6.5 Resource levels and the number of drugs in the portfolio

Resource level (US$M)	Number of drugs per portfolio	Number of possible portfolios
Unconstrained	6	1
500	3	20
750	4	15
900	5	6

Once the number of drugs capable of being supported at each resource level had been identified, all the possible drug combinations (a total of 42) were generated and Monte Carlo simulations carried out for each drug combination. Appendix A provides the corresponding list of portfolios and their composition. To determine the number of simulation runs required to reach convergence, running averages of the results were monitored until they levelled off. For each of these portfolios, 380 simulations were required to achieve convergence. The order in which the drug candidates were taken into clinical development was determined by the market value of each drug (estimated patient population x estimated price). The tool was programmed to start with the drug that had the highest market value and once all the drug candidates were in the development process, the resources were allocated on a first-come-first-served basis (Table 6.6).

Frequency distributions of the estimated performance measures were generated and various statistics computed to aid the decision-making process. The results were used to construct the efficient frontier as described earlier (Section 6.2) for each resource level.

Table 6.6 The market value of the drugs and the ranking based on it

Drug candidate	Market value (US$)
D	1,029,000,000
A	523,224,000
B	426,880,000
C	409,860,000
F	48,664,000
E	30,660,000

6.3.4 Results and discussion

6.3.4.1 Portfolio with all six drugs

The first set of results shown in Figures 6.4 and 6.5 provides an insight into the probability of making a profit from the portfolio of all six drugs without any resource constraints. In Figure 6.4, there are no instances where all six make it to the market. The most probable situation is getting just one drug into the market (30%) followed by two (22%). These probabilities are consistent with those of Reichert (2004). The author states for murine and humanised MABs the overall rate of success varies from 14% to 26%. As the majority of the drugs fail, the one(s) that does make it to the market have to bear the cost of the failed drug(s).

Using the probabilities of failure used in the Monte Carlo simulations (Table 4.11) the number of drugs that fail for each one that does make it successfully to the market can be calculated. The cumulative rate of success for a MAB is 0.823 x 0.547 x 0.667 x 0.777 = 0.233. Therefore the average number of failed MABs per successful MAB is 1/0.233 = 4.3. DiMasi *et al.* (2003) and Myers and Howe (1997) have taken a similar approach to accommodate the cost of failed drugs in calculating the cost of drug development. This means that each MAB that enters the market has to bear the cost for 4.3 failed MABs. This feature is demonstrated in the distribution of the expected NPV in Figure 6.5, where most of the portfolio NPV values turn out to be negative due to investment losses.

Figure 6.6 presents another output of the tool; the risk profile of the portfolio with six drugs. The probability of not making a profit (a negative NPV) for this particular

portfolio is 58 %. On the positive side, the successful commercial launch of all six drugs brought in an expected NPV of over US$ 900 million. These results indicate the nature of the biopharmaceutical drug development process that is encountered by the industry and highlights the importance of making the right choices in selecting drug candidates for clinical development, using limited resources.

In reality resource constraints will be applied to drug candidate selection. The next section describes the results from the Monte Carlo simulations carried out under the influence of resource constraints to construct the efficient frontier.

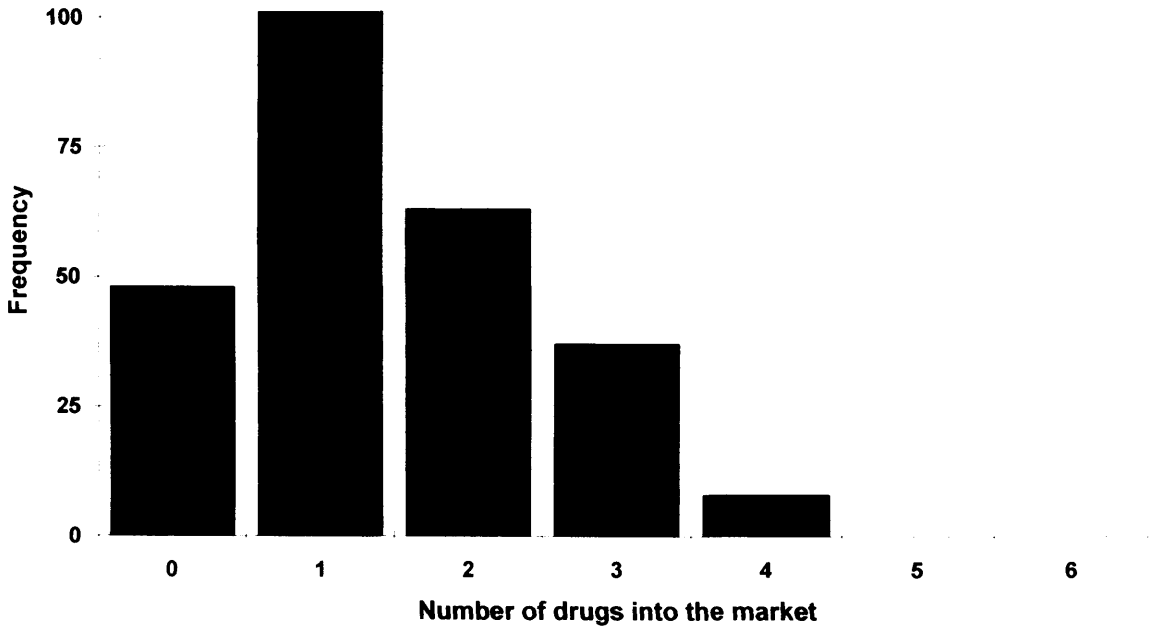


Figure 6.4 The number of drugs that make it to the market from a portfolio of six is presented. The highest probability is for just one drug to make it to the market and there are no instances where all six drugs have made it despite no resource constraints being applied.

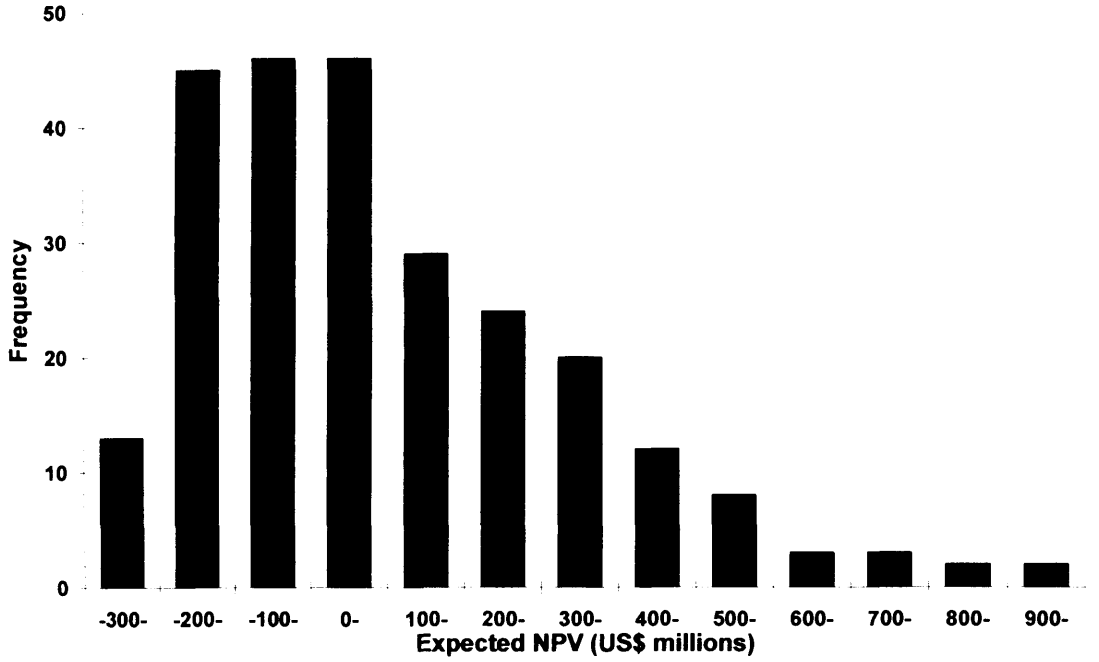


Figure 6.5 NPV distributions for the portfolio with all six drugs and an unlimited level of resources. There is a wide distribution of the NPV values and majority of the NPV values are negative

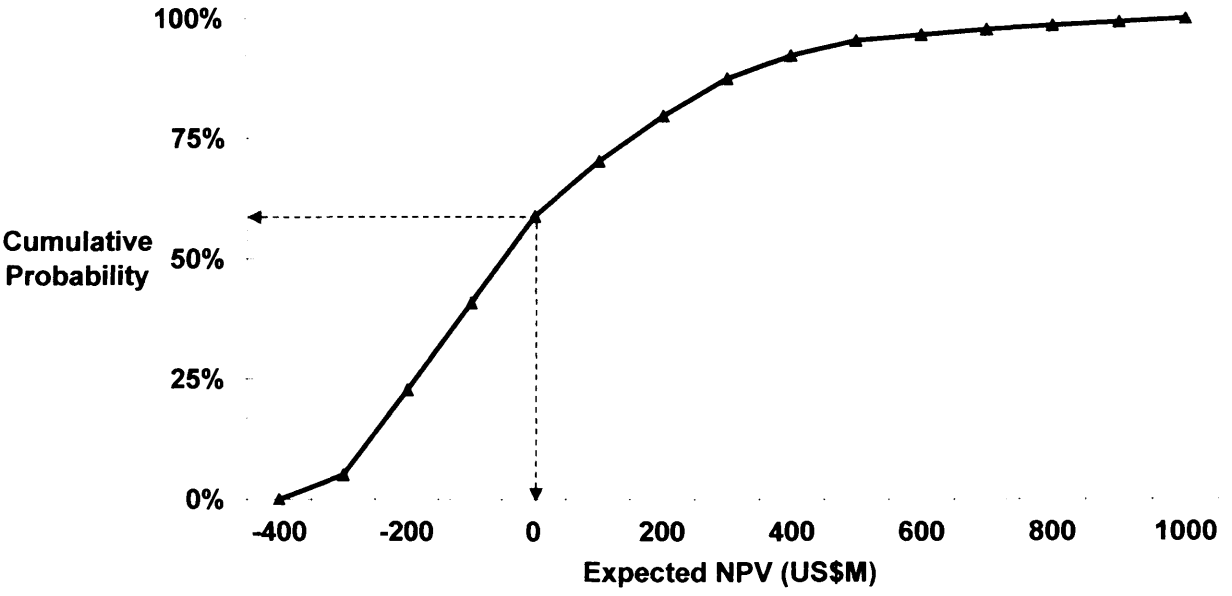


Figure 6.6 Risk profile for the portfolio with all six drugs and unconstrained resource levels. The probability of making a negative NPV for this particular portfolio is 58%.

6.3.4.2 Efficient frontier

a) Efficient frontier for US$500 million resource level

The expected NPV values and risks computed for each of the portfolios for the US$ 500 million resource level are presented in Figure 6.7. Portfolios with negative expected NPVs (7 out of 20) were excluded.

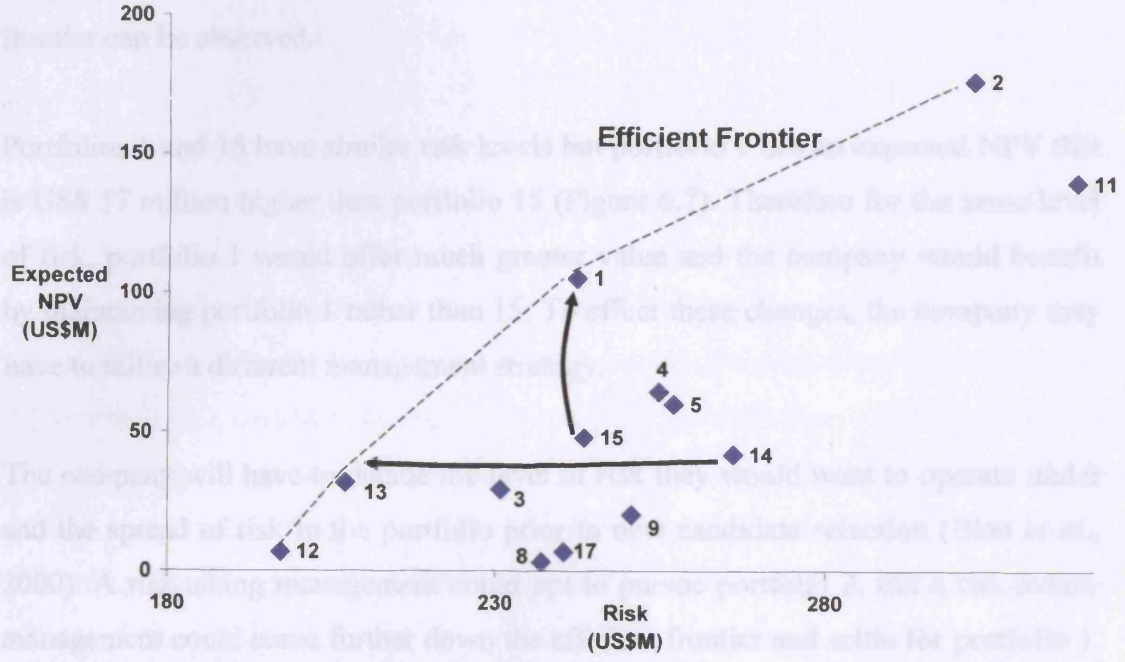


Figure 6.7 Efficient frontier for US$ 500 million resource level. Portfolios 12, 13, 1 and 2 form the 'efficient frontier' for this particular resource level.

As there are only 20 portfolios possible at this resource level, the number of points on this efficient frontier diagram is limited. The reward (expected NPV) as well as the risk of the simulated portfolios changes within a wide range according to the combination of drugs held in the portfolio (Figure 6.7). Portfolios 13 and 14 have almost the same expected NPV, but portfolio 14 has a much higher level of risk (US$ 59 million greater). Therefore it is a safer option to have portfolio 13 in clinical development rather than 14. In this hypothetical case study, this would require the company to drop drugs D and E and bring in drugs C and F. Drugs D and E could be outsourced in order to diversify the risk taken by the company.

If changing the portfolio composition is not an option, other strategic moves could be applied. For example as the risk and reward of a portfolio has been quantified, steps could be taken to add value and reduce risk. To add value other indications can be

pursued. To reduce the risk, a higher number of tests could be carried out earlier in the development pathway, thereby reducing the chance of late stage failure. This type of explicit consideration of the alternative projects will help create a management strategy for the company that would add long-term value to the company portfolio (Keelin and Shew, 2003). These changes can then be added to the model and by carrying out simulations the movement of the portfolio relative to the efficient frontier can be observed.

Portfolios 1 and 15 have similar risk levels but portfolio 1 has an expected NPV that is US$ 57 million higher than portfolio 15 (Figure 6.7). Therefore for the same level of risk, portfolio 1 would offer much greater value and the company would benefit by maintaining portfolio 1 rather than 15. To effect these changes, the company may have to utilise a different management strategy.

The company will have to decide the level of risk they would want to operate under and the spread of risk in the portfolio prior to new candidate selection (Blau *et al.*, 2000). A risk-taking management could opt to pursue portfolio 2, but a risk-averse management could come further down the efficient frontier and settle for portfolio 1. The difference between these two portfolios is that drug C in portfolio number 1 is replaced by drug D (highly risky, potential blockbuster) in portfolio 2. This single change brings about an increase of the risk by US$ 59 million but the expected NPV rises by US$ 71 million. This type of insight is not obvious at the outset and would be an asset to decision-makers.

b) Efficient frontier at higher resource levels

The reward and risk distributions for the portfolios for US$ 500 and 750 million resource levels of resources are presented in Figure 6.8. The results indicate that increasing the number of drugs in a portfolio by virtue of having a greater financial resource does not necessarily result in an increase in the expected NPV. This is because a higher number of drugs mean more capital has to be invested, which in turn increases the costs the portfolio has to recover to make profits. This is further confirmed by the yields of the portfolio containing all six drugs. This has an expected NPV of only US$ 6 million and a risk of US$ 260 million.

As before the risk is reduced by an increase in the number of drugs. For example portfolio 2 is the highest in value under the US$ 500 million resource constraint and portfolio 36 is the highest under the US$ 900M constraint (Figures 6.8 and 6.9). While there is a drop in the expected NPV from portfolio 2 to 36 of US$ 122M, there is also less risk (US$ 26M) involved with portfolio 36 than 2. Risk-averse management may prefer portfolio 36, provided they can generate the additional resources, in order to spread the risk.

By considering just the market value (patient population x drug price), portfolio 21 (Appendix 1) would be expected to be the highest yielding of the portfolios if US$ 750 million of resources were made available. However, the results show that the expected NPV of portfolio 24 is US$ 8 million higher than 21. This demonstrates the unreliability of static values to estimate the value of a project and the importance of factoring in uncertainty and risk into the portfolio evaluation. Adding drug C to portfolio three (which results in portfolio 22) increases the expected NPV by US$ 26 million and reduces the risk by US$ 4 million. This type of information could be utilised by the management for raising required funds in order to increase the number of drugs in its portfolio.

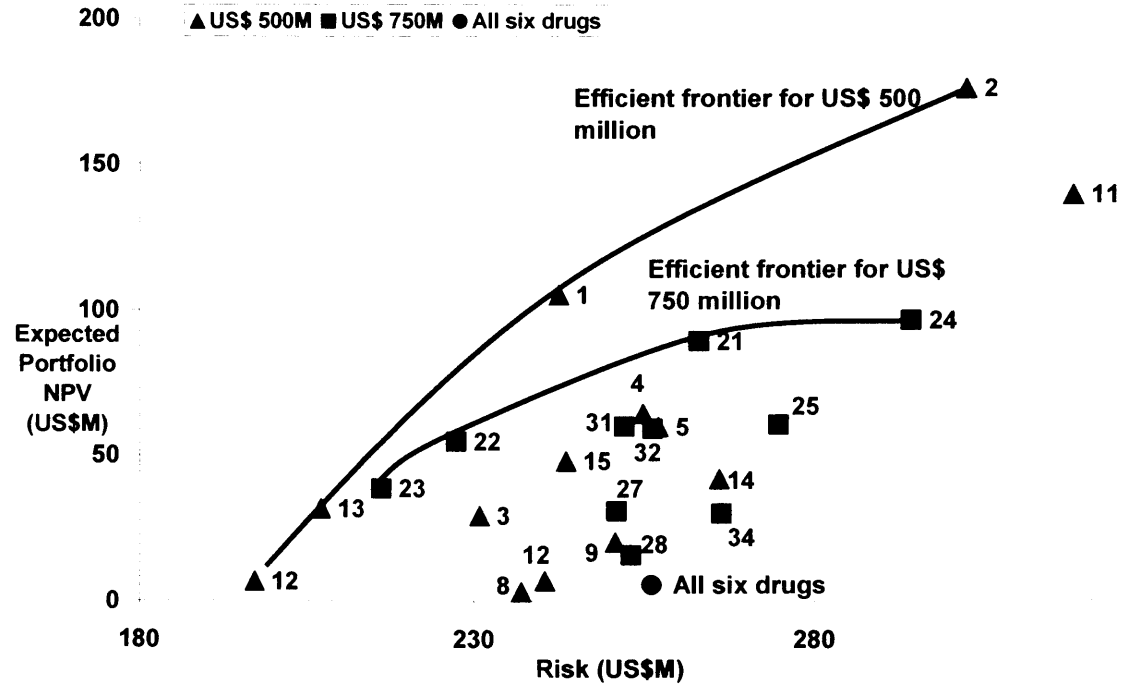


Figure 6.8 The risk and reward distributions for the portfolios for US$ 500 and 750 million resource levels. For comparison the portfolio with all six drugs have been included.

The results also enable the effect of different drugs on the portfolio value and risk to be compared. For example, replacing drug E with F at a US$ 750 million resource level (portfolio 31 and 32) does not bring about a significant change in risk or reward. This allows the company to select the drugs strategically. For example a company may choose a drug in a new therapeutic area in order to gain confidence of investors and regulators or align with the core competencies of the company. In comparison to all the other portfolios, the portfolio with all six drugs has the lowest expected NPV and a medium level of risk. Therefore, even if the resources existed it would be strategically important to outsource some of the drugs in order to reduce the risk and increase the value.

Figure 6.9 presents the expected NPV and the associated risk for a US$ 900 million level of resources. The strategy by which the value of the portfolio could be increased is demonstrated. By replacing drug F in portfolio 39 with C (portfolio 36) the value could be increased by US$ 17 million and the risk reduced by US$ 7 million. Again, the portfolio of six drugs is quite far away from the efficient frontier. Finally, as an illustration of further analysis that can be carried out by the tool, the risk profiles for three selected portfolios are discussed.

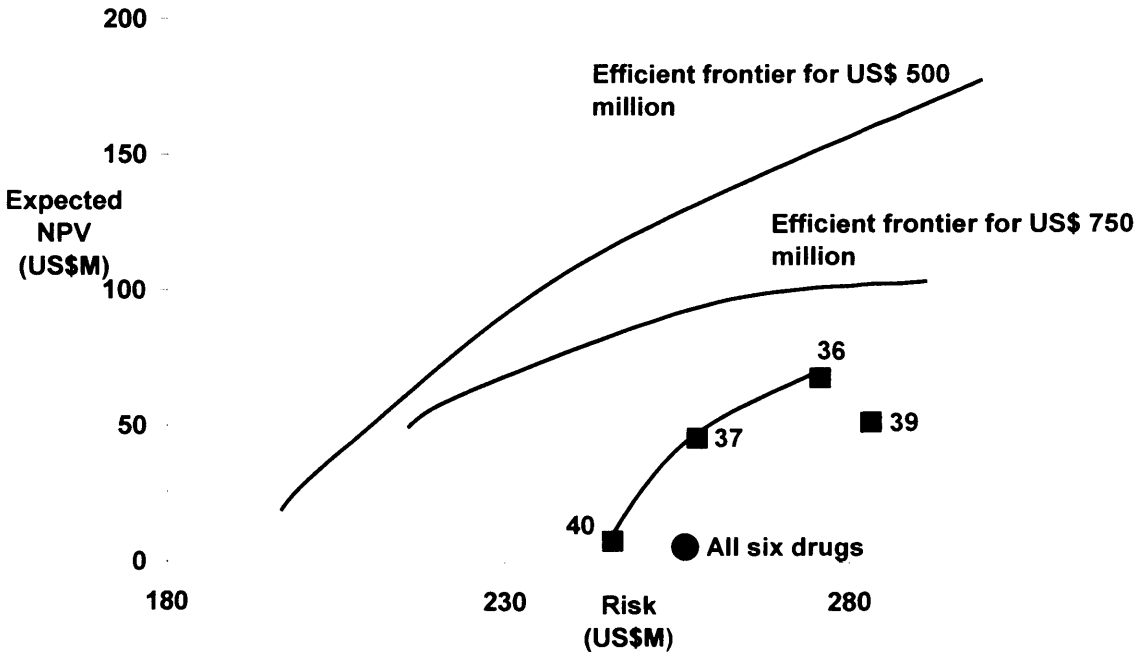


Figure 6.9 The efficient frontier for US$ 900 million resource level. For comparison the portfolio with all six drugs has been included. With the increase in the number of drugs in the portfolio, the NPV has reduced.

6.3.4.3 Portfolio risk profiles

The risk profiles for the portfolio with the highest expected NPV in each resource category are presented in Figure 6.10. The probability of losing money (negative NPV) due to the uncertainty or risk of failure for portfolio 2 is 28.2%. This is known as the "downside risk" of the portfolio (Stonebraker, 2002) and is the lowest of all the portfolios taken into consideration in Figure 6.10. With a higher number of drugs (portfolio 24 and 36) the probability of not making a profit is higher (45 and 50% respectively). These results help to compare further and distinguish between the portfolios. Stonebraker (2002) uses a risk profile for a single drug candidate to compare against the company benchmarking in deciding whether to proceed with development work or not with that particular candidate. For portfolio 2, the probability of making a positive NPV is 17 – 22% higher than portfolios 24 and 36 respectively.

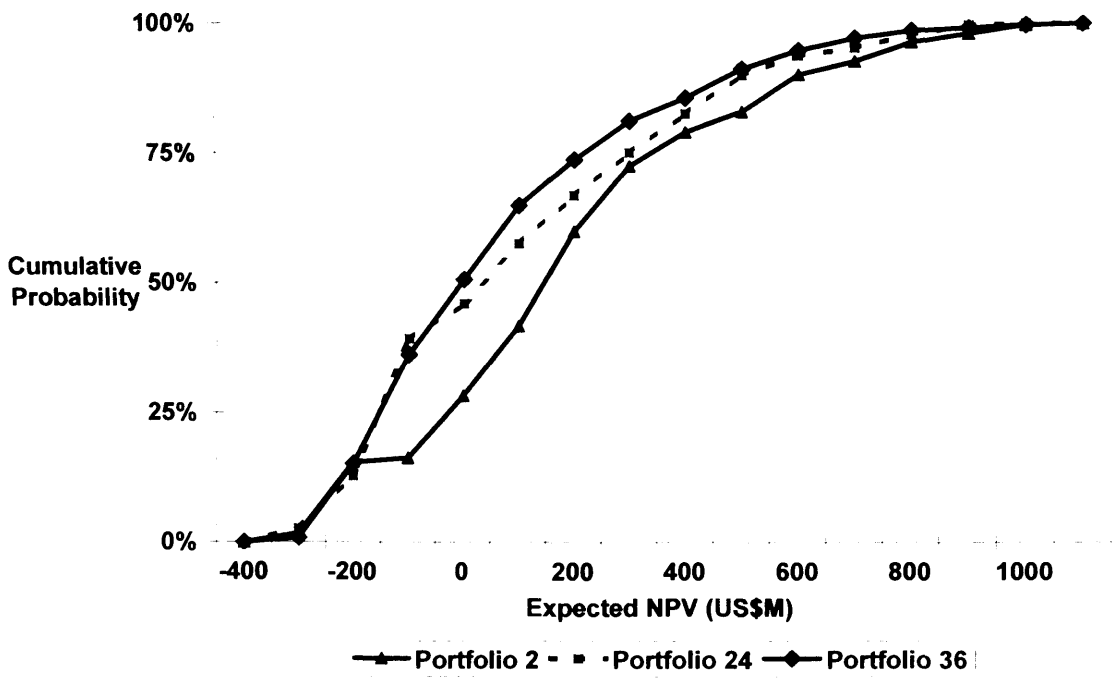


Figure 6.10 Risk profiles for portfolio 2, 24 and 36. With the increase in the number of drugs in the portfolio, the probability of making a negative NPV increases.

These outputs could be compared to internal standards to decide on whether to proceed with a project portfolio or not. Stonebraker (2002) states that Bayer Pharmaceuticals find a downside risk value of 20% to be low relative to similar projects. Portfolio 2 has an upside potential (a maximum NPV) of US$ 900 million.

Taking all of the results into consideration, portfolio 2 appears the best for the company to start off with since, although it is risky, it provides high returns for a lower level of resources. The data gathered from the simulation can be used for further analyses, which can be used to understand the dynamics of drug development. Similar risk analysis can be carried out on a single drug candidate or concentrate on one phase for the full portfolio.

6.4 CONCLUSIONS

To remain competitive companies must deploy their capital effectively and in ways that maximise returns and minimise risk (Walls, 2004). Decisions made on a project-by-project analysis and ignoring the diversification affects often yield sub-optimal results. This chapter has presented a method to compute the value of different portfolios while taking the uncertainty in the parameters of drug development into consideration. This was followed by the application of the tool to quantify the risk and reward of different drug portfolios in a biopharmaceutical company. The uncertainties in the R&D and the market have been captured in a single simulation.

Through this method, decision-makers will be able to identify clearly where the company portfolio is positioned with regard to risk-return characteristics of alternative product portfolios and hence make appropriate investments based on limited resources. The flexibility of the tool to model different types of distributions allows uncertainty in drug development to be captured appropriately. When more information is available with the progress of development work, the simulations could be repeated. With the inputs having less uncertainty; by comparing the new position of the portfolio relative to the former position, informed decisions could be made about the portfolio composition and portfolio management strategy.

The goal of portfolio analysis is to enable senior management and teams to have better conversations about important decisions and not to provide the answer (Keelin and Shew, 2003). The type of results and analysis presented in this chapter will enable such dialogue to take place by quantifying the risk and reward within a portfolio.

CHAPTER 7

CONCLUSIONS AND FUTURE WORK

7.1 INTRODUCTION

The ever-expanding field of biopharmaceuticals requires that companies add value to their organisation at all levels. The product pipelines of companies are in a constant state of flux, where new drugs are identified and existing drugs are either discontinued from development or launched into the market. The cost of biopharmaceutical drug development has been on the increase during the past several decades. This increase in costs, along with the pressures from managed healthcare organisations means that the companies are under pressure to manage strategically their research and development activities. The risk and uncertainty inherent in the drug development process provides further challenges in trying to take a drug from discovery into the market under a finite level of resources. Simulation tools can be used to enhance the decision-making process in managing the drug development process strategically. This chapter summarises the efforts made in this thesis to prototype such a tool to model the drug development activities. Future work that could advance the understanding of this topic is also discussed.

7.2 OVERALL CONCLUSIONS

The main focus of this thesis has been the design and implementation of a decision-support tool that captures the technical, operational and financial aspects of biopharmaceutical drug development, as well as incorporating the effects of risk. As an illustration, the tool was used to simulate the development of monoclonal antibodies, from discovery to commercialisation. The decision-making and management process of drug development were reviewed in Chapter 1 in order to understand the type of information required from such a tool and to identify the deficiencies of current methods. An investigation of the drug development process enabled the activities that are involved in biopharmaceutical drug development to be defined (Chapter 2). While the application of the tool was demonstrated through

modelling the development of monoclonal antibodies, it is generic in its approach and could be used for modelling of any biopharmaceutical, for example, recombinant proteins.

The modelling approach adopted in this thesis allows modellers to address explicitly the technical and business aspects of biopharmaceutical drug development. The conceptual framework and the implementation process presented in Chapter 3 allow for different management strategies of development activities to be prototyped before implementation. Key indicators of profitability such as cost of development, time to market and net present value (NPV) of the portfolio of products are computed as aids to decision-making. A key point in this tool is that it aims to provide a frequency distribution showing the probability that a project's NPV will exceed a certain level, rather than a simple point estimation. The resulting prototype tool combines interactive graphics, animation, risk analysis and dynamic simulation to create a flexible environment for modelling the drug development pathway.

The benefits of the hierarchical nature of the framework were highlighted; the framework confers maximum flexibility since it permits tasks to be modelled at different levels of detail, according to the aims of the user. Resource usage profiles generated by the tool for renewable as well as non-renewable resources help identify bottlenecks and periods of under-utilisation of resources. The ability to view the simulation process through a graphical user interface eases the debugging process. The costing takes into account the activities as well as resources such as facilities. The ability to assign distribution probabilities instead of point values allows the modelling of uncertainties. Risk of failure at different stages of the drug development pathway has been incorporated into the model, allowing Monte Carlo simulation technique to be carried out for risk analysis. Investment assessments could be based on both the expected outcome and the likelihood of achieving certain critical values. Industrial expert knowledge has been crucial in establishing a base case set of assumptions, specified as defaults values in the framework in a database to be used when populating the model for a simulation. These values and the simulation process were described in Chapter 4.

The application of the tool for modelling the process of development of a portfolio of monoclonal antibodies was presented on Chapter 5. A sensitivity analysis was performed to identify the key parameters in drug development. This was used to set the probability distributions when performing risk analysis in the latter sections of the thesis. The sensitivity analysis was followed by a scenario analysis to observe the effect of changing just two specific input parameters while keeping all the others constant. The contour plots generated allows the decision-makers to understand the consequences of changes to these parameters due to the uncertainty present in drug development. A case study was then carried out to whether to build a manufacturing facility or to contract out the manufacture of material for clinical trials and the market. Assigning distribution parameters and performing Monte Carlo simulations took the uncertainty in drug development into account. Advice from industrial experts was used to verify the inputs and validate the outputs of the tool. The case study highlighted the importance of taking uncertainty into account when evaluating different options in planning drug development activities. Methods of presenting and analysing information generated by the simulations were suggested.

In Chapter 6, the application of the tool to compute the reward and risks of different product portfolios was demonstrated. A method to generate an efficient frontier of product portfolios through Monte Carlo simulations was suggested and implemented. The prototype tool was then used to perform the necessary simulations and construct the efficient frontier under the influence of different resource levels. This allowed different product portfolios to be compared on a risk-reward basis and informed decisions be made in new drug candidate selection. Risk profiles for different portfolios were generated to understand the risk faced by a company seeking to apply resources to develop a selected set of drug candidates. This type of information provides the management with an insight into the portfolio management problem in order to make informed decisions. In summary, the chapter demonstrated how simulations could be used to develop and manage a product portfolio.

The work in this thesis highlights the benefits of adopting an integrated approach to the process-business interface in biopharmaceutical manufacture. This has been realised through the design and application of a simulation tool. During and after data gathering, the layout of the simulation model serves as a platform for

communication between different departments within a company such as process development, manufacturing, accounting and management. Such a model could therefore aid in understanding how a process really works. Effective use of the simulation results can be used to streamlining the company's resources according to the demands. This will in turn lead to concentrated R&D efforts, more effective use of resources, faster time-to-market and improved returns on investment. The applicability of the model has been demonstrated through several case studies.

7.3 FUTURE WORK

The framework and methods developed in this thesis contribute to the emerging field of computer-aided design tools that integrate process and business perspectives of biopharmaceutical manufacture. It also provides a base for further work; several such examples are discussed next.

In addition to the work presented in this thesis, parallel work (Lim *et al.*, 2003; Mustafa *et al.*, 2004) has concentrated on modelling the manufacturing process of biopharmaceuticals. Using a hierarchical approach, the manufacturing process has been modelled in detail. By integrating this detailed manufacturing model with that of biopharmaceutical drug development, the development process could be viewed from a more detailed manufacturing perspective. Such integration should allow the impact of manufacturing on the development process to be studied better.

An increase in the level of detail at which the drug development is modelled will help to add value to the data generated. The hierarchical structure allows new levels to be added to the model. A detailed model of the manufacturing process of development work can be added in order to achieve better results. The process of scheduling manufacturing and development tasks can be added in order to provide the optimal schedule for a selected portfolio of drugs. For ease of implementation, the clinical trials were modelled in a simple manner. For example, by adding the ability to model clinical trials being carried out at different locations, the challenges faced, such as logistics could be planned better.

The structure of the company could be modelled more explicitly, with a breakdown of the management and the other staff. This will allow a more detailed resource

utilisation profile to be generated. However the increase in the level of detail will add to the size of the model and slowdown the simulation time. Therefore steps will have to be taken to quicken the simulation tasks along with the new additions to the tool.

One of the main challenges in developing this prototype tool has been to gather data to use as default values for inputs. Developing a database of such drug development data would help in any work to be carried out in the future. Data such as time lengths, costs and failure rates can be collected through literature, databases maintained by regulators such as USFDA and through discussions with industrial experts.

The real options method used to decide on the composition of the product portfolio is proving to be popular in the industry (Nichols, 1994; Doctor *et al.*, 2001; Rogers *et al.*, 2002; Rogers *et al.*, 2003). In the option pricing theory, it is assumed that a project can be treated as a stock option and conceptually the project under evaluation is being treated as it were a separate company with a defined value of stock. Adding the capability to perform real options analysis to the tool will enhance the tool's ability to help in decision-making.

The work in this thesis illustrates the benefits of risk analysis, using the Monte Carlo simulation technique. The effect of uncertainty in many parameters was demonstrated. However, there are other uncertainties in the development and commercialisation of biopharmaceuticals, such as transportation and storage of products. By adding the ability to model the impact of different locations for manufacturing and sales, the different economic conditions in locations, for example, Europe vs. USA, can be captured. This would also allow multi-site investment decisions, e.g. how much to be invested where, to be simulated. Generating sales and inventory planning profiles would broaden the scope of decision-making for this tool.

Regarding the modelling of activities, more rigorous and predictive models can be developed. More advanced mathematical methods to capture the activities and risks could be applied. For example, operations management literature could provide methods to model the efficiency of process development personnel and scheduling

methods could be included to help planning manufacturing activities. The optimum methods of incorporating these more rigorous models into the tool need to be investigated. Increasing the optimisation capabilities of the tool is also suggested. The use of mathematical methods, such as mixed integer linear programming can be investigated. Incorporating multi criteria decision-making will also add value to the outputs of the tool.

The case studies presented in this thesis demonstrate the advantages of taking into account the technical, operational and financial consideration in drug development planning. Further simulation studies using the tool could test new strategies such as different clinical trial methods. Further, the mergers and acquisitions occurring in the industry today could be modelled to identify the possible advantages a company would have in pursuing such an option.

The software package used, Extend Industry Suite v5, was found to be appropriate for modelling the drug development process. The simulation times were kept to a reasonable value. However with additional components being added, the time length for a simulation could increase considerably and will pose a problem. The optimisation capabilities of Extend Industry Suite v5 was found to be inadequate as it allowed a limited number of parameters to be included.

In conclusion, the future work that has been outlined draws upon the framework and methods established in this thesis. The development of more sophisticated models and the opinion of industrial experts would improve the accuracy of prediction. The future will see tools such as the one described in this thesis be used more frequently in order to aid decision-making.

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APPENDIX A
Data for case study in Chapter 6

This section provides the information used for the case study in Chapter 6. The portfolio compositions are presented in Table A.1 and the distribution parameters are outlined below.

Table A.1 Portfolio names and compositions

Portfolio name	Drug candidates	Portfolio name	Drug candidates
1	ABC	22	ABCE
2	ABD	23	ABCF
3	ABE	24	ABDE
4	ABF	25	ABDF
5	ACD	26	ABEF
6	ACE	27	ACDE
7	ACF	28	ACDF
8	ADE	29	ACEF
9	ADF	30	ADEF
10	AEF	31	BCDE
11	BCD	32	BCDF
12	BCE	33	BCEF
13	BCF	34	BDEF
14	BDE	35	CDEF
15	BDF	36	ABCDE
16	BEF	37	ABCDF
17	CDE	38	ABCEF
18	CDF	39	ABDEF
19	CEF	40	ACDEF
20	DEF	41	BCDEF
21	ABCD	42 (full portfolio)	ABCDEF

Table A.2 Distributions assigned to the drug candidates for the market share value

Drug candidate	Number of annual patients	Probability (%)
A	185,760	10
	247,680	30
	309,600	40
	371,520	20
	433,440	10
B	7,680	5
	10,240	10
	12,800	70
	15,360	10
	17,920	5
C	34,400	10
	43,200	30
	54,000	40
	64,800	20
	75,600	10
D	41,160	15
	54,880	20
	68,600	30
	82,320	20
	96,040	15
E	4,380	10
	5,840	30
	7,300	40
	8,760	20
	10,220	10
F	9,240	10
	12,320	20
	15,400	50
	18,480	20
	21560	10

Table A.3 Probability distributions assigned to the drug price for each drug candidate

Drug candidate	Price per patient per treatment (US$)	Probability (%)
A	1,014	10
	1,352	30
	1,690	40
	2,028	20
	2,366	10
B	43,800	5
	58,400	10
	73,000	70
	87,600	10
	102,200	5
C	4,554	10
	6,072	30
	7,590	40
	9,102	20
	10,626	10
D	9,000	15
	12,000	20
	15,000	30
	18,000	20
	21,000	15
E	2,520	10
	3,360	30
	4,200	40
	5,040	20
	5,880	10
F	1,896	10
	2,528	20
	3,160	50
	3,792	20
	4,424	10

Table A.4 Distributions assigned to the drug candidates for the development time value

Drug candidate	Development time for PI, PII and PIII (months)	Probability (%)
A	12, 6, 6	20
	15, 9, 9	50
	24, 18, 18	30
B	0, 0, 6	15
	0, 0, 9	80
	0, 0, 18	05
C	12, 9, 9	20
	18, 12, 12	50
	24, 18, 18	30
D	12, 12, 12	20
	18, 18, 18	40
	24, 24, 24	40
E	9, 9, 9	20
	12, 12, 12	50
	15, 15, 15	30
F	12, 12, 12	10
	18, 12, 12	70
	24, 18, 18	20

Table A.5 Distributions assigned to the drug candidates for the clinical trial time value

Drug candidate	Development time for PI, PII and PIII (months)	Probability (%)
A	9, 12, 18	20
	12, 18, 24	50
	18, 24, 30	30
B	9, 12, 18	15
	12, 18, 24	80
	18, 24, 30	05
C	9, 12, 18	20
	12, 18, 24	50
	18, 24, 30	30
D	9, 12, 18	20
	12, 18, 24	40
	18, 24, 30	40
E	9, 12, 18	20
	12, 18, 24	50
	18, 24, 30	30
F	9, 12, 18	10
	12, 18, 24	70
	18, 24, 30	20

Table A.6 Distributions assigned to the drug candidates for the product yield

Drug candidate	Yields for PI, PII and PIII (g/batch)	Probability (%)
A	150, 450, 945	20
	100, 300, 630	50
	50, 150, 315	30
B	150, 450, 945	15
	100, 300, 630	80
	50, 150, 315	05
C	150, 450, 945	20
	100, 300, 630	50
	50, 150, 315	30
D	150, 450, 945	20
	100, 300, 630	40
	50, 150, 315	40
E	150, 450, 945	20
	100, 300, 630	50
	50, 150, 315	30
F	150, 450, 945	10
	100, 300, 630	70
	50, 150, 315	20

Table A.7 Distributions assigned to the drug candidates for the delays in manufacturing material

Drug candidate	Delays for PI, PII and PIII (months)	Probability (%)
A	3, 3, 3	20
	0, 0, 0	50
	6, 6, 6	30
B	3, 3, 3	15
	0, 0, 0	80
	6, 6, 6	05
C	3, 3, 3	20
	0, 0, 0	50
	6, 6, 6	30
D	3, 3, 3	20
	0, 0, 0	40
	6, 6, 6	40
E	3, 3, 3	20
	0, 0, 0	50
	6, 6, 6	30
F	3, 3, 3	10
	0, 0, 0	70
	6, 6, 6	20

Table A.8 Distributions assigned to the drug candidates for the changes in cost of goods value for the production of the material for the market

Drug candidate	Cost of goods (US$/gram)	Probability (%)
A	1,200	20
	1,500	50
	1,800	30
B	720	15
	900	80
	1,080	05
C	800	20
	1,000	50
	1,200	30
D	600	20
	750	40
	900	40
E	1,440	20
	1,800	50
	2,160	30
F	1,280	10
	1,600	70
	1,920	20

APPENDIX B
Paper by the Author

Rajapakse, A.; Titchener-Hooker, N. J.; Farid, S. Modelling of the Biopharmaceutical Drug Development Pathway and Portfolio Management. In *Computer-Aided Chemical Engineering: ESCAPE-14*; Barbosa-Póvoa, A., Matos, H. (Eds); Elsevier Science B.V.: Lisbon, 2004; Vol. 18